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DYSPHAGIA LUSORIA: CLINICAL ASPECTS IN THE ADULT*

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DYSPHAGIA lusoria is the term which for years has been applied to symptomatic esophageal compression by an *arteria lusoria.* An *arteria lusoria* is an anomalous form of the right subclavian artery (figure 1). It arises as the fourth branch of an otherwise normal aortic arch, and passes around the left and posterior aspects of trachea and esophagus, before coming to lie in the proper position to serve as the subclavian artery. This appears to be the most common anomaly of the aortic arch system, its incidence having been recorded upon anatomic study as 0.6%,[1] 0.8%,[2,3] 1%[4] and 1.8%.[5] One radiologic study of 8,500 subjects showed an incidence of 0.15%.[6] There is frequent association with other aortic arch and heart anomalies, particularly the tetralogy of Fallot,[7,8] coarctation[9,10] and patent ductus arteriosus.[8] Surgical correction of some major heart defects may be made more difficult by the presence of an *arteria lusoria.*[7] An *arteria lusoria* may accompany anomalies of the esophagus itself.[11]

Embryologically, an *arteria lusoria* represents the persisting distal descending portion of the fourth right branchial arch, there having been obliteration of the proximal arch, in reverse of the normal situation.[12] The *arteria lusoria,* then, takes off directly from the aortic arch, just beyond the origin of the left subclavian artery. The first portion of the *arteria lusoria* is often dilated at its origin, this representing the remnant of the posterior branch of the right aortic arch. The dilatation received its classic interpretation at the hands of Kommerell,[13] and it has been named for him.

In about 20% of cases[6] there are variations from the usual course of

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the artery. The "type encerclant" of Segers and Brombart [6] arises as the first branch of the aorta and almost completely encircles trachea and esophagus before passing on to the shoulder. In another variation, the *arteria lusoria* passes between trachea and esophagus.

The roentgen signs of pressure upon the esophagus (figure 2), usually best studied in the right anterior oblique projection, are those of a pulsating oblique extrinsic pressure defect passing upward from left to right, just above an aortic knob impression which at times is unusually small.[14-19] The de-

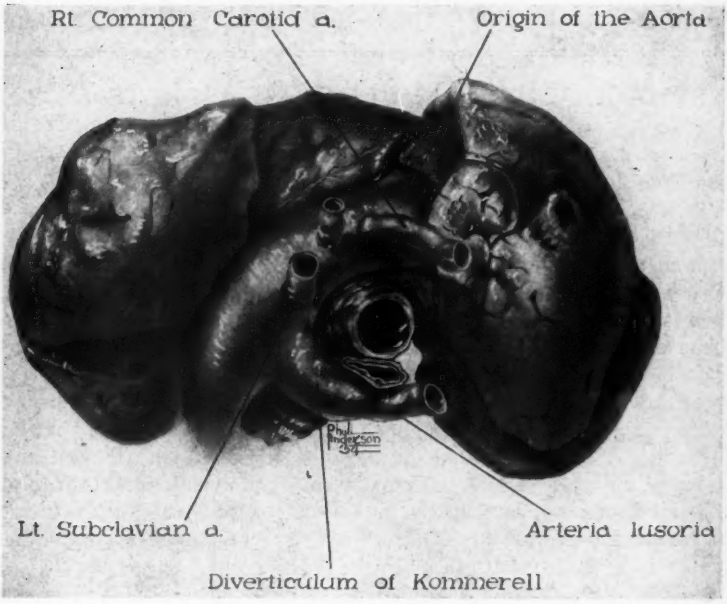

FIG. 1. Presentation of the anatomic relationships of the *arteria lusoria* and diverticulum of Kommerell, as viewed from above.

pression in the esophagus may be unexpectedly large because it is actually the diverticulum of Kommerell, when present, which makes esophageal contact (figure 3). Arterial catheterization is feasible for detailed roentgen study.[20]

The purpose of this report is discussion of clinical experiences with dysphagia lusoria as encountered in personally observed patients whose symptoms began during adult life. The anatomic, embryologic and radiologic aspects have been presented in detail in the wonderful monographs of Segers and Brombart,[6] Evans,[21] Poynter,[22] Holzapfel [1] and Cairney.[12]

Clinical Material

Eleven patients with the diagnosis of dysphagia lusoria have been studied. These were instances of "pure" dysphagia lusoria, the only cardiovascular anomaly being the presence of an *arteria lusoria,* as best the point could be determined by clinical and radiologic examination. In none of the patients

Fig. 2. Characteristic esophageal defect, as studied roentgenologically in the two oblique projections.

was the anomaly viewed at operation or autopsy. Four of the 11 patients were women and seven men. Two were Negroes.

In four patients no other significant diagnosis was established. In two an important degree of arteriosclerosis was present, and another had compensated hypertensive heart disease. Other discharge diagnoses were chronic bronchitis, sarcoidosis, duodenal ulcer and situational depression.

During the period of study the radiologic diagnosis of *arteria lusoria* was made incidentally in 21 other patients who had no symptoms referable to the esophagus.

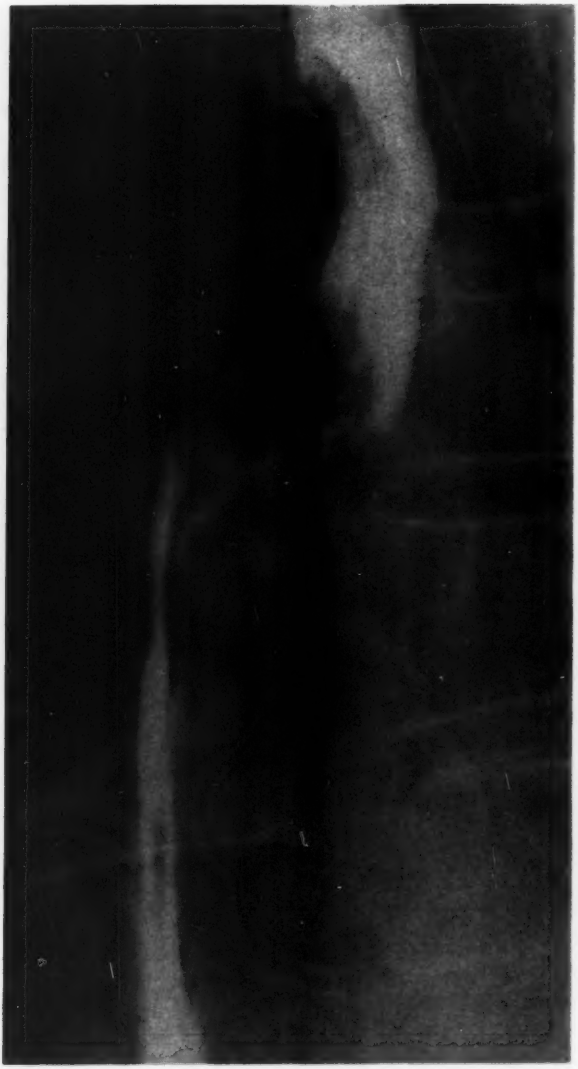

FIG. 3. When a diverticulum of Kommerell is present, the impression upon the esophagus is much larger than one might expect.

Clinical Picture

Each of the 11 patients sought help primarily because of dysphagia. Three patients stated that the onset had seemed rather sudden, while the others were not able to state exactly when they had first noticed swallowing difficulty. Three patients had been in the third decade of life when the first trouble was experienced, two in the fourth decade, three in the fifth, and one each in the sixth, seventh and eighth decades. One patient had had unexplained spells of choking and syncope when a small child.

These patients struck one as being miserable with their common problem of swallowing difficulty. None was very sick objectively, but his day-to-day symptoms, an unexplained source of fear, had led to disabling worry and depression. Seven had been symptomatic more than a year at the time the diagnosis was established, and one had had symptoms for 10 years. The three points which were regularly reiterated during the interviews were disability, fear and fatigue.

The dysphagia as described by all of the patients was the simple sensation of temporary arrest of solid boli beneath the manubrium. There was difficulty with liquids if they were taken rapidly. There was no pain other than the discomfort of substernal fullness which regularly accompanies obstructed swallowing. The dysphagia was a constant, daily problem.

Other symptoms were inconsequential. One patient had a mild oppressive sensation deep in the middle of the chest most of the time. The patient with duodenal ulcer had the classic complaints of that disease superimposed on the dysphagia. In two cases there was chronic cough, but it could not be concluded that chronic bronchopulmonary infection due to periodic aspiration is a complication of dysphagia lusoria, as it may be in other forms of esophageal obstruction. Rather, it was believed that there was enough tracheal obstruction [9] from the *arteria lusoria* to produce bronchial irritation. This was not true dyspnea lusoria.

Physical examination gave no findings which could be ascribed to the anomaly or its effects. In particular, the findings which have been described in this disease were absent: murmur of arterial compression, inequality of upper extremity pulses, evidence of thoracic duct obstruction, and trophic changes in the right arm. It was interesting that the swallowing time was normal in each of the eight patients in whom it was studied.

The diagnoses were established by the characteristic esophageal defect as demonstrated roentgenologically. Esophagoscopic examination proved important in excluding the main radiologic differential problem, benign extramucosal esophageal tumor; and in searching for other esophageal disease which may cause dysphagia, particularly esophagitis and hiatus hernia. None of these was found among the 10 patients who were studied esophagoscopically. The imprint of the *arteria lusoria* could not be recognized endoscopically in two cases. In six the indentation involved mostly the left segment of the esophageal circumference, while in two the posterior aspect

showed the most deformity. It was apparent to the endoscopist that the extrinsic mass was pulsatile in four patients, but in the other four the rhythmic motion of the mass could not be differentiated from transmitted cardiac pulsations.

Although dysphagia lusoria is a clear-cut mechanical problem which is cured with assurance by resection of the physiologically expendable arterial segment,[23-26] operative treatment was decided against in all cases. When the very slowly progressive nature of the course of the disease and the absence of complications were balanced against the seriousness of the operation, it was concluded that surgical treatment should be withheld, pending nonoperative therapeutic efforts. This, of course, meant that it was not possible to offer the patients quick concrete therapy. It was found, however, that there was much to contribute in terms of explanation about the cause of symptoms, the nature of the abnormality, and the benignancy of the future course. Detailed explanation of the x-ray films to the patient proved to be an effective therapeutic gesture.

Comment

Clinically, dysphagia lusoria and the obstructive manifestations of some other arterial anomalies become of importance either during the first two or three years of life or much later, in adult life.[27-32] The former is more common, and this is easily understood. That a constricting arterial anomaly at times remains clinically latent until adulthood is explained by the fact that the diameter of major arteries normally continues to increase after neighboring structures have attained maximal size. In some patients, onset of symptoms appears to be explained by arteriosclerotic or hypertensive changes in the arteries about the base of the heart. But in spite of an incidence of *arteria lusoria* of about 0.75%, clinically important obstructive manifestations are unusual, and dysphagia lusoria is rarely encountered in gastroenterologic practice.

These patients were an unhappy group when they came to the hospital for help. Their fear—especially, of course, of cancer—their discouragement, and the fatigue engendered by the constancy of symptoms at first seemed enough to justify surgical therapy. As a most interesting observation of the present study, however, it was found that detailed discussion and instruction were sufficient in themselves to provide satisfactory therapy, at least for the moment. The nature of the trouble was easy to present and easy to understand. The fact that the abnormality must have been present since birth was accepted quickly, and this automatically supplied tremendously reassuring support. The possibility of surgical correction was mentioned to some of the patients, but, after the mechanism of their dysphagia was understood, none considered this the wisest course. It was particularly gratifying to the patient to find that with this understanding his symptoms improved. This was, perhaps, because some of the tenseness left his de-

glutitory efforts. To the doctor, it appeared probable that patient acceptance would have to be stimulated by periodic reassurance for a long time.

Conclusions

Dysphagia lusoria is due to esophageal compression by an anomalous right subclavian artery. Symptoms may not appear until late adult life. The subjective illness may be most disabling, but the internist can furnish satisfactory relief in some cases by detailed and sympathetic explanation of the abnormality. Experiences with 11 patients are discussed.

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A STUDY OF CHOLECYSTECTOMY *

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THE ability to visualize the normally functioning gall-bladder by appropriate radiographic technics has made it possible for the practitioner of internal medicine to make the diagnosis of a surgical disease with considerable frequency and to be forced to advise for or against the removal of the gall-bladder. This diagnosis may be made during a routine physical check-up, in the course of study for some other disorder, or in the face of symptoms directly referable to the biliary tract. Whatever the circumstances, the patient will usually look to his physician for guidance and for some expression of opinion as to the consequences of surgical intervention. In the majority of instances this guidance will be based on information remembered somewhat dimly from medical school, or distorted by recent and usually limited experience, pleasant or otherwise. Our study was initiated in an effort to determine how the passing years and improving technics, as well as the advent of the antibiotics, have changed the course of the patient undergoing cholecystectomy. It also gave a means of appraising the gross results of this procedure and evaluating to some extent the relative meticulousness of the operating surgeons, as a group, that have done these cholecystectomies. Many more gall-bladders have been removed by surgeons in practice than by members of the house staff, but these have not been considered separately, and no effort has been made to single out any group of operators for particular attention. This is simply a reflection of cholecystectomy with and without common duct exploration as done in a University hospital.

TABLE 1

Cholecystectomies
1934—1953

Year	Without Duct Exploration	With Duct Exploration	Total
1. 1934–1938	171	19	190
2. 1939–1943	204	17	221
3. 1944–1948	210	38	248
4. 1949–1953	285	62	347
Total	870	136	1006

A total of 1,006 cholecystectomies have been done during the 20 years 1934–1953, inclusive (table 1). Of these, 136 were accompanied by a

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common duct exploration. During this series of four five-year periods there has been a steady increase in the total number of procedures carried out. The difference in these periods lies principally in the change in hospital stay of the patient and in the postoperative morbidity and mortality.

It was felt that in studying the hospital stay per patient only operations not followed by definite complications should be considered, since in some instances the individuals with serious postoperative disturbances were hos-

TABLE 2

Average Hospital Stay in Days

	Year	Cholecystectomy Alone	Cholecystectomy Plus Exploration
1.	1934–1938	15.2	15.9
2.	1939–1943	12.2	13.3
3.	1944–1948	10.7	12.1
4.	1949–1953	8.3	14.4

pitalized for months, and this would distort the picture of the typical case (table 2). There has been a gradual decline in the duration of hospitalization of the patient with a simple cholecystectomy, and the average stay now is short. The rather remarkable fact that there has been no change in the stay after cholecystectomy with associated exploration of the common duct is probably a reflection of the cautious nature of the surgeon. Most of these patients have had "T" tube drainage of their common ducts after exploration, and there is a necessary time lag in closing off this drainage tube, obtaining

TABLE 3

Morbidity after Operation
(Average in Days)

Group	Number of Patients	Cholecystectomy	Number of Patients	Cholecystectomy Plus Exploration
1.	141	2.1	15	3.8
2.	174	2.0	11	2.7
3.	181	1.6	18	1.5
4.	260	1.2	52	3.0
Total	756	1.6	96	2.8

cholangiograms, and being certain that bile is passing through the reëstablished common duct and that all is generally well.

In this group having relatively uneventful removal of the gall-bladder, and with the associated choledochotomies a record was made of morbidity. For the purposes of our study we accepted as morbidity any elevation of temperature over 100° F. after the day of operation (table 3). The morbidity as determined in this fashion has never been especially high for simple cholecystectomy. It has been somewhat greater for the added injury of

exploration of the common duct, but has not been extreme in any of the five year periods studied. This group of patients does not include those who have experienced any clinically demonstrable postoperative complication, but simply those who have had a low grade fever of undetermined origin occurring during the postoperative period. This is 85.0% of the total group studied.

The remaining 15% is more interesting, for these offer the opportunity for improvement and change (table 4). This group is composed of the 25 fatalities in the series, and 129 postoperative complications of such magnitude as to be diagnosed. It is evident that with the simple cholecystectomy there is small hazard to life (1.8%). In those instances where surgical exploration of the common duct was indicated the mortality and the incidence of complications have both decreased in the last five year period (1949–1953). The relative incidence of complications and deaths following simple removal of the gall-bladder and following removal done with an associated exploration of the common duct remains the same. It is evident, then, that while there have been real technical improvements, the hazard associated with opening the common duct when indicated essentially doubles the occurrence of complications and deaths.

TABLE 4

Incidence of Complications

	Normal	Complications	Deaths
(A) After Cholecystectomy			
1.	141	28 (16.4%)	2 (1.2%)
2.	174	23 (11.2%)	7 (3.4%)
3.	181	24 (11.4%)	5 (2.4%)
4.	260	23 (8.1%)	2 (0.77%)
Total	756	98 (11.3%)	16 (1.8%)
(B) After Cholecystectomy Plus Exploration			
1.	15	2 (11.0%)	2 (11.0%)
2.	11	5 (29.4%)	1 (5.9%)
3.	18	16 (42.2%)	4 (10.5%)
4.	52	8 (15.4%)	2 (3.9%)
Total	96	31 (22.8%)	9 (6.7%)

So much, then, for the fact that these procedures are not without a very real risk in the hands of the surgeons who have performed them in this hospital. What is the nature of the complications following surgery, and of what cause do these patients die? There were 98 patients who, after simple cholecystectomy, had some serious disturbance of their postoperative course. The record of each of these individuals was reviewed and the apparent cause of their difficulty determined. Forty-nine of these complications were systemic in character, 33 local and related to the immediate

operative field, 16 listed as miscellaneous (table 5). The systemic complications were largely pulmonary in character, and many of the febrile courses recorded as bronchopneumonia in the 1930's would now be diagnosed as atelectasis and possibly never recorded on the chart. There were seven instances of thrombophlebitis which were not fatal, and seven urinary tract infections of varying magnitude. The local complications have been more serious in most instances. There have been four wound disruptions,

TABLE 5

Nonfatal Complications after Cholecystectomy

(A) Systemic	
Pulmonary	32
Cardiac	3
Peripheral vascular	7
Urinary	7
(B) Local	
Wound infection	15
Wound disruption	4
GI disturbances	3
Hemorrhage	4
Bile leakage	5
Jaundice	2

an incidence of 0.46%, which is not excessive. Of the four instances of severe postoperative hemorrhage, only one required surgical intervention to control the bleeding. Two patients exhibited an increasing jaundice after surgery. One of these subsided spontaneously in the hospital without pain. The other patient apparently passed a stone, after leaving the hospital against advice, and both patients are now well and free of symptoms seven years after surgery. The leakage of bile listed made itself manifest as either a

TABLE 6

Cause of Death after Cholecystectomy

Subdiaphragmatic abscess	2
Myocardial infarct	1
Pyelophlebitis	1
Pneumonia	2
Pulmonary embolism	2
Peritonitis	5
Miscellaneous	3

collection of bile in the wound or a subphrenic abscess, and in these instances was successfully drained.

The deaths following simple cholecystectomy are disturbing to examine (table 6). There were two instances of subphrenic abscess, both following operation for chronic cholecystitis. The death from myocardial infarction took place on the operating table. The figures on death from generalized peritonitis are not so gloomy as they might appear, since three of these patients had associated gastric resections for ulcer or malignancy. There were only two deaths following cholecystectomy for acute cholecystitis, the

one from pyelophlebitis, the other on the second postoperative day in an individual who never aroused from her anesthetic.

The character of complications following cholecystectomy with associated exploration of the common duct is much the same as that previously described. There were 11 systemic complications, mostly pulmonary. The local complications (table 7) were unusual in that none of the 136 patients had a wound disruption. There were five individuals with continuing evidence of common duct obstruction after surgery. One of these apparently

TABLE 7

Nonfatal Complications after Cholecystectomy Plus Exploration of Common Duct

(A) Systemic	
Pulmonary	7
Cardiac	1
Urinary	3
(B) Local	
Wound infection	4
Abscess	3
GI disturbances	2
Jaundice	5
(C) Miscellaneous	6

passed a stone from the common duct after surgery, and her jaundice subsided and she has remained symptom-free for the past six years. The other four were reëxplored. In two patients stones were removed, in a third a hypertrophied sphincter of Oddi was found and a sphincterotomy performed. All these patients are now well. In most instances the deaths after exploration were a reflection of the very poor condition of the patient at the time surgery was performed (table 8). Of the four patients who died from shock, three were found to have had an extensive hemorrhage at or after the

TABLE 8

Causes of Death after Cholecystectomy Plus Exploration of the Common Duct

Pyelophlebitis	2
Peritonitis	1
Shock	4
Subdiaphragmatic abscess	1
Miscellaneous	1

time of surgery. The two deaths from pyelophlebitis were in individuals who had acute cholecystitis with common duct obstruction at the time of surgery.

There are a few points which deserve special comment. In this 20 year period only one patient has been re-admitted for common duct obstruction after a cholecystectomy without exploration. This patient had a partial cholecystectomy for acute cholecystitis, and returned two and one-half years later at which time the remainder of the gall-bladder was removed and a stone was removed from the common duct. Except for the patient described

previously under the complications of cholecystitis as having possibly passed a stone postoperatively, there has been no suggestion of postoperative common duct obstruction in the hospital. During this time there have been three individuals in whom the common duct was inadvertently divided during the removal of the gall-bladder. In all three instances the error was recognized and a primary repair carried out at the time. All of these have had no evident ill effects from their experience. This represents the most tragic error that can be made at the time of cholecystectomy and serves as an example of the fact that it can be corrected. There is no evidence to show that in any person the common duct has been left obstructed at the time of discharge from the hospital. There is no known instance of postoperative stricture of the common duct in this series. The other common and tragic error associated with cholecystectomy is ligation of a major branch of the hepatic artery. There is no evidence to show that this has been done at any time during the past 20 years in this hospital.

In summary, then, a series of 1,006 cholecystectomies carried out at the Vanderbilt University Hospital has been reported. The incidence of common duct exploration is about the same as that in other major hospitals throughout the country. The mortality rate in individuals requiring exploration of the common duct is high but is a reflection of the relatively poor physical condition in which many of these patients come to the hospital. The mortality rate in simple cholecystectomy has dropped satisfactorily during the past 20 years, and while the operation is still not without an appreciable risk, the risk is not excessive today.

TREATMENT OF GENITOURINARY MONILIASIS WITH ORALLY ADMINISTERED NYSTATIN *

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THE widespread use of the broad spectrum antibiotics has intensified the problem of clinical infections caused by *Candida albicans.*[1] These infections—moniliasis of the mouth, vulvovaginal mucosa, intertriginous areas of the skin, and the nails—have been common and persistent in the face of many modes of therapy. The recognition that some of the broad spectrum antibiotics enhance the virulence of *C. albicans* and result in its systemic dissemination has made the search for effective anti-monilial agents one of great importance.[2, 3] Such an agent might effectively prevent the aggravated and even fatal fungus infections which have been reported as having complicated antibiotic therapy.[1]

Nystatin is an antifungal substance produced by the growth of a soil actinomycete, *Streptomyces noursei.* It was first reported in 1951 by Hazen and Brown under the name of fungicidin.[4, 5] Since that time studies have shown Nystatin to have a potent inhibitory effect on many pathogenic fungi, including *Candida albicans.*[6] Further investigation demonstrated a remarkable ability of this drug to clear, or markedly reduce, *C. albicans* from the intestinal tracts of laboratory animals and humans,[6] and to protect laboratory animals from the effects of the lethal combinations of the tetracyclines and *C. albicans.*[2, 3]

While the oral administration of Nystatin has been shown to control effectively the yeastlike flora of the intestinal tracts of humans,[6] there has been no previous report of the effect of this drug on lesions outside of the gastrointestinal tract when the drug is given by mouth. The purpose of this paper is to present five cases of genitourinary moniliasis, all of which were treated with orally administered Nystatin.

The diagnosis of moniliasis was made in each case by the microscopic identification of the yeast-forms of *C. albicans* in moist preparations. The specimens for examination were either exudates from the lesions or sediment from freshly catheterized and centrifuged urine.

CASE REPORTS

Case 1. A 34 year old white female with polycystic kidneys had had a succession of episodes of pyelonephritis. She had been treated with a wide assortment of antibiotics and antibacterial agents, including oxytetracycline, penicillin, tetracycline, Gantrisin, Furadantin and erythromycin. Following a rather prolonged course of therapy the patient developed intense vulvar itching with an erythematous, erosive, well defined eruption involving the vulva and spreading out over the contiguous areas

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of the thighs and up along the inguinal folds. Monilia was identified in the sediment of a centrifuged urine specimen and, later, from the exudate of the eroded areas.

Therapy with gentian violet, infrared light, and hydrocortisone with neomycin was unsuccessful, and the lesions became progressively more extensive.

A course of Mycostatin (Nystatin-Squibb) was started. The patient was given one tablet of 500,000 units three times daily, by mouth. In five days the lesions were completely cleared except for slight residual erythema. This faded in the subsequent few days.

About two weeks after the Mycostatin was discontinued there was a recurrence of the vulvitis with intense itching. This again responded rapidly to Mycostatin administered by mouth in the above mentioned doses.

Case 2. A 56 year old white female had had monilial vulvovaginitis for three years. She had been treated by numerous physicians with numerous medicaments, including gentian violet, as well as with roentgen-ray therapy. The latter provided some transient relief, but for the most part the patient was in much discomfort.

Yeast forms were identified in the surface exudate of the eroded lesions. Mycostatin, one tablet by mouth three times daily, was prescribed. The vulvar lesions had completely cleared by the eighth day of therapy. The medication was discontinued at this time. About one week later the patient again began to notice the vulvar itching, and on examination some erythema of the labia minora was seen, and the characteristic white plaques of monilia were noted on the prepuce of the clitoris. Mycostatin was resumed, with clearing of these small lesions in three days.

This patient has discontinued the drug on four occasions, and has each time suffered a relapse of the vulvitis. The vulvitis has always cleared promptly upon resumption of therapy. At this writing the patient has taken Mycostatin almost continuously for three months.

It is noted, incidentally, that a rather intractable cheilosis, which had not responded to large doses of B-complex vitamins given by injection, did subside during therapy with Mycostatin. While monilia were not demonstrated in the fissured lesions (it didn't occur to the writer that monilia might have been their cause), one wonders if perhaps the cheilosis was caused by *C. albicans,* and if its disappearance may represent a response to the fungicide.

Case 3. A 73 year old white female complained of scalding urine and intense vulvar itching. She was found to have diabetes mellitus, which condition was controlled with diet and insulin. Microscopic examination of the urinary sediment showed a moderate pyuria, with some budding yeast forms also noted. Urine culture demonstrated the presence of *Staphylococcus albus.* Gantrisin was administered and the scalding decreased. Urine examination showed that the pyuria had disappeared. However, the vulvar itching persisted, and yeast forms were identified in the vaginal discharge.

Mycostatin was given by mouth in a dose of one tablet three times daily. There was gradual improvement of the vulvitis over a period of 17 days. The drug was discontinued, and thus far the patient has remained free of vulvitis.

Case 4. A 57 year old white female had a six year history of urinary frequency, urgency, strangury, and lower abdominal cramps, which were relieved by voiding. Past treatment had included irrigations of the bladder, antibiotics and antibacterials, and repair of a cystocele. None of these measures gave much or prolonged relief to the patient.

Examination of the urinary sediment showed only two to three white blood cells per high power field. Three budding yeast forms were seen in the corresponding fields. Mycostatin, one tablet three times daily by mouth, was prescribed.

In one week the urgency and strangury had disappeared but the frequency persisted. In 20 days the frequency was relieved to the extent that the patient went for

stretches of from four to six hours between voidings. The patient has been continued on the medication without interruption, at her request.

Case 5. A 32 year old white female developed intense vulvovaginitis while in the hospital recovering from an ovarian cystectomy. Preoperatively and postoperatively she had received oxytetracycline. The vulvovaginitis was treated with sulfonamide cream, without benefit.

A wet preparation of the vaginal secretions was examined microscopically. Among the profusion of pus cells and debris, scattered yeast forms could be identified.

Mycostatin, one tablet three times daily by mouth, was given. In one week the vaginal discharge had subsided and the vulvitis was markedly improved. The patient discontinued the medication and in about 10 days had a relapse, with profuse vaginal discharge and intense vulvar itching. Another course of therapy was initiated. The discharge and itching were quickly controlled and the vulvar inflammation has shown considerable improvement. The improvement has been maintained, but complete clearing has not yet been achieved after two months of therapy.

Conclusion and Summary

A potent fungicide, Nystatin, has been administered orally to five patients with genitourinary moniliasis. Each case has responded with rapid improvement of the symptoms. Objective improvement has in some cases been less prompt and less complete.

There is a high incidence of relapse when the medication is discontinued. Retreatment has been as successful as the initial courses of therapy.

One instance of clearing of chronic cheilosis of undetermined origin, possibly monilial, was an incidental observation. No adverse reactions to the drug were noted.

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A CLINICAL STUDY OF POLIOMYELITIS IN THE TROPICS *

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INTRODUCTION

THE epidemiologic aspects of poliomyelitis in the tropics have been described in the past by Sheplan,[1] Allwood-Paredes,[2] Irazabal,[3] Andrade Marin,[4] Seddon,[5] Paul,[6] McFarlan [7] and Rosen,[8] and recently have been reemphasized by Paul.[9] A review of the literature, however, fails to disclose any corresponding clinical studies of this disease in native populations in the tropics. We are therefore reporting a clinical study of poliomyelitis carried out during an outbreak of that disease in El Salvador in July and August of 1953.

The use of the word "tropics" in this paper should be explained. Considered geographically, the tropics lie between the lines of Cancer and Capricorn. Considered climatologically, the tropics connote a hot, humid, doldrum-producing climate. However, within the vast geographic tropics, climate can vary widely, with truly temperate weather being present in large areas. Considered medically, the tropics connote areas where a large variety of protozoan and metazoan parasitic diseases are common. But "tropical diseases" occur in such nontropical areas as Japan, Korea, North China and North Africa. Considered culturally, the tropics connote large populations living under primitive conditions of housing, clothing, diet and medical care. Considered from all these points of view, El Salvador is a tropical country, but "poliomyelitis in the tropics" can be present in areas not tropical by all four criteria of climate, geography, medicine and culture.

DESCRIPTIVE DATA [9-12]

El Salvador is located 13 to 14 degrees above the equator in Central America. It is bounded on the north and west by Guatemala, and on the south and east by the Pacific Ocean and Honduras. The country, measuring only 140 by 60 miles, is crossed by two mountain ranges that run from east to west, with average elevations of 2,200 feet but with maximal elevations of 7,000 feet. Because of these elevations the climate, except in the lowlands along the Pacific coast, is temperate, with an average annual temperature of 75 degrees. There is minimal year-round fluctuation in temperature, and only two seasons are distinguished: the rainy, from May to October, and the dry, from November to April. The country is densely

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populated with about 2,000,000 people, of whom 10% are white (almost all Spanish in origin), 40% Indian, and 50% mixed. The occupation of the people is predominantly agricultural in nature, the two main crops being coffee and sugar. A large part of the population lives in quite primitive conditions of housing, sanitation, clothing, diet and medical care. In the two largest cities, however, there are excellent medical and hospital facilities.

Clinical Data

Poliomyelitis generally occurs the year round in El Salvador, with a few cases reported every month of the year.[2] Outbreaks of larger numbers of cases have occurred in the recent past [2] and in this present instance. Figure

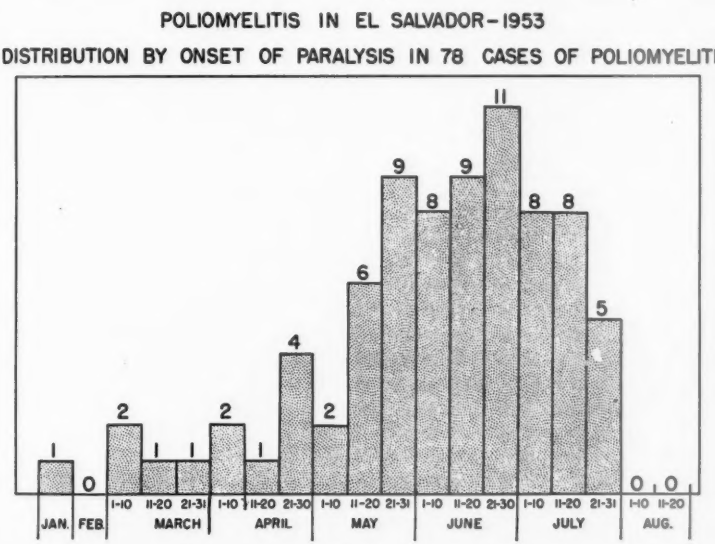

Fig. 1.

1 shows the number of cases occurring during 10 day periods from the beginning of the epidemic until the end of the study in the group examined by us. A total of 100 patients was examined on referral from the Ministry of Health after having been reported to that office as cases of paralytic poliomyelitis. These patients were all examined and some hospitalized in a polio ward established for that purpose in Hospital Rosales in the capital city of San Salvador. Of these 100 cases referred for examination, 22 were found after limited study to have other diseases (table 1). These figures compare favorably with the percentage of mistaken referral diagnoses in hospitals in the United States.

The symptoms which the patients presented most commonly in this out-

break are recorded in table 2. In considering these symptoms, special notice should be taken of two factors of selection that occurred, one on our part and the other on the part of the virus. It has already been pointed out that the Ministry of Health had referred patients reported as poliomyelitis on the basis of paralysis, and these cases therefore would presumably represent the more severe infections. Second, as shown in table 4, the vast majority of

TABLE 1

Poliomyelitis in El Salvador: Diagnoses in 100 Patients Studied

Diagnosis	No. of Cases	Total
Poliomyelitis		78
Other diseases:		
Cerebral palsy	5	
Postencephalitic state	2	
Rheumatic fever	2	
Brain tumor with papilledema	2	
Acute febrile disease	1	
Mumps encephalitis	1	
Encephalitis, unclassified	1	
Convulsive disorder	1	
Arteriovenous fistula of the leg	1	
Coma, cause undetermined	1	
Bell's palsy, old	1	
Hysteria	1	
No disease	3	22
		100

patients were in the very young age groups, in which the symptoms would represent only those complaints manifest to the mother, whether or not the child could verbalize his discomfort. Accepting these conditions, poliomyelitis in this outbreak was almost always a febrile illness, followed a few days after onset by paralysis which seemed to improve rather rapidly and for which two thirds of the patients had some sort of treatment. The illness

TABLE 2

Poliomyelitis in El Salvador: Common Symptoms in 78 Cases of Poliomyelitis

Symptoms		Per Cent of Cases
Weakness of one or more extremities		100
Fever		93
Improvement in paralysis after onset		70
Treatment prior to examination		66
(a) Hot packs	47%	
(b) Antibiotics	28	
(c) Exercises	11	
(d) "Injections"	10	
(e) "Vitamins"	10	
(f) Massage	9	
Two or more days' illness prior to onset of paralysis		62
Diarrhea		46
Stiff neck		37
Chills		36
Vomiting		36
Pain		24

TABLE 3

Poliomyelitis in El Salvador: Uncommon Symptoms in 78 Cases of Poliomyelitis

Symptoms	Number of Cases
Cough	5
Dyspnea	3
Sore throat	2
Triple vaccine inoculation	2
Headache	1
Somnolence	1
Restlessness	1
Adenoidectomy (14 days prior to onset)*	1
Hoarseness*	1

* Not explicitly inquired for in history forms.

was also accompanied in nearly half of the cases by diarrhea; in a little more than a third by stiff neck, chills and vomiting; and in about a fourth of the cases by pain. The illness was not characterized by a number of symptoms (table 3) which experience in the United States had led us to inquire for explicitly, the most notable of which are cough, sore throat and headache. Neither somnolence nor restlessness occurred in any numbers. In one case adenoidectomy had been performed 14 days prior to onset of illness. Two cases had received pertussis-tetanus-diphtheria vaccine within 14 days of

TABLE 4

Poliomyelitis in El Salvador: Physical Findings in 78 Cases of Poliomyelitis

Findings		Per Cent of Cases
Age	Less than 2 years of age	70
	Less than 3 years of age	85
Sex	Male	54
	Female	46
Muscle weakness		86
Days from onset of paralysis to time of examination		
10 days or less		17
Between 11 and 30 days		22
More than 30 days		53
Unknown or unrecorded		8
Elevated temperature		33
Complicating illness		15
Hamstring or back muscle spasm		10
Stiff neck		10

onset, and in one of these patients weakness occurred in the injected extremity.

The physical findings in these cases are shown in table 4. A further factor of selection should be borne in mind in considering these findings. As shown in finding 4, in most cases a considerable period of time had elapsed from the onset of paralysis to the time of examination, and this lapse was more than a month in 53% of cases. One would expect this delay to reduce the incidence of those findings seen during the acute stage

of illness. If this additional condition is accepted, poliomyelitis during this outbreak would furthermore be an illness in the very young age groups, occurring slightly more frequently in the male, with paralysis of such mild degree that almost 50% of cases had single extremity involvement and over 10% had no residual weakness at time of examination (table 5). A third

TABLE 5

Poliomyelitis in El Salvador: Location of Muscle Weakness in 78 Cases of Poliomyelitis

	Number of Cases	Per Cent of Cases
One extremity:		
One arm	2	
One leg	36	49
Two extremities:		
One arm and one leg	3	
Two arms	2	
Two legs	15	25
Three extremities:		
Both legs and one arm	1	
Both arms and one leg	1	3
Four extremities	3	4
Neck only	1	1
Cranial VII only	2	3
None	12	15

of the cases were found to have an elevated temperature, and a tenth to have spasm or stiff neck. Three cases had complicating pneumonias, and three had impetigo. There were two instances of malnutrition and anemia, and one case each of salmonella enteritis, inguinal hernia and measles. Bulbar poliomyelitis, manifested by facial palsy only, was seen in three cases. In only three cases were all four extremities involved, and there were no deaths.

TABLE 6

Poliomyelitis in El Salvador: Cerebrospinal Fluid Findings in 78 Cases of Poliomyelitis

Number of Cases	Number with Lumbar Punctures	Interval Between Onset of Paralysis and Lumbar Punctures	Number Abnormal	Number Normal	Per Cent Abnormal
78	33	Less than 7 days	10	1	91
		From 8 to 14 days	5	1	87
		From 15 to 21 days	1	1	50
		Over 21 days	3	11	21
Total			19	14	

Abnormal cerebrospinal fluid findings:

Increased white cells only	0
Increased protein (30–153 mg. %)	15
Increased cells and protein (48–300 cells)	4

Laboratory Data

The cerebrospinal fluid findings are shown in table 6, and when these data are considered the foregoing conditions should be kept in mind. A total of 33 of the 78 cases of poliomyelitis had lumbar punctures, of which 19 were abnormal. Of these abnormal fluids, protein was elevated in all 19 cases (normal for the laboratory, less than 30 mg. %), and cells were increased in four of these 19 cases (normal, less than seven cells per cubic millimeter).

Treatment

A total of about 40 patients were hospitalized in the ward established for poliomyelitis cases. Most of these were patients in the acute phase of illness, but some needed additional diagnostic studies or were sufficiently ill with complications to require hospitalization. An outpatient physical therapy clinic was established for nonhospitalized cases. Physical therapy on in-patients and out-patients was carried out by two physical therapists acting as consultants for the United States. The management of the hospital ward, the direction of the physical therapy clinic, and consultation by orthopedic surgeons on all patients were later taken over by local physicians.

Discussion

The clinical features of poliomyelitis in this outbreak seem to us to be remarkably different from those seen in current outbreaks in this country. However, in a single study in this country by Weinstein and coworkers,[18] a type of polio infection was distinguished in a particular age group that is quite similar to the illness described in this paper. On the basis of (1) the clinical features of polio infection in this particular age group in the temperate areas; (2) the clinical features of polio in general in the tropics in this and another study,[14] and (3) the epidemiologic differences between infection in the tropics and the temperate regions,[9] it seemed possible to us to distinguish two illnesses caused by the same virus infection, "infantile paralysis" and "poliomyelitis." These differences are contrasted in table 7.

When these two illnesses are distinguished, "infantile paralysis" would seem to be the type of infection that existed from early Egyptian times [15] to the 1880's, when the first epidemics occurred. It would seem also that the tropics are the last site where this type of illness occurs in "pure culture." It is noteworthy that, at least in El Salvador, the casual observer can still see typical poliomyelitic deformities in an adult from an illness occurring when epidemics were unknown, which is a characteristic aspect of poliomyelitis infection during the long period of history mentioned above.

The very recent appearance of epidemics in the tropics generally [19] suggests that these areas may be in the same stage as Europe was in 1887 when Medin described the first outbreak of poliomyelitis infection involving 44

TABLE 7

Poliomyelitis in El Salvador: Contrasting Features of "Poliomyelitis" and "Infantile Paralysis"

	"Poliomyelitis"	"Infantile Paralysis"
Season	Late summer[9]	Year around[9]
Climate	Temperate or arctic[9]	Warm or tropical[9]
Sanitation	Good[9]	Poor
Age	Adults chiefly	Children chiefly
	50% over 15[9]	55–70% under 2[9]
	25% over 30[9]	75–85% under 3[9]
Antibodies	Present later in life[9]	Present early in life[9]
Sex	More females[13]	More males[13]
Effect of pregnancy	Predisposes to paralysis[16]	Illness not seen in pregnant women
Skin eruptions	Relatively common[13]	Rare
Chills	Common[13]	Relatively uncommon
Stiff neck	Common[13]	Relatively uncommon
Single extremity paralysis	Rare	Common
Multiple extremity paralysis	Common	Rare
Bulbar polio	Relatively common[13]	Rare
Difficulty in swallowing	Relatively common[13]	Rare
Paralysis ocular movement	Relatively common[13]	Rare
Paralysis of respiratory muscles	Relatively common[13]	Rare
Difficulty in urination	Relatively common[13]	Rare
Severity of illness	Severe[13]	Mild
Case fatality rate	7–10%[17–18]	0–2%[17–18]

cases in Stockholm. One wonders if this is the beginning of a change in the tropics from the clinical illness of "infantile paralysis" to "poliomyelitis."

Mention has already been made of the limitations of this clinical study in El Salvador. On the basis of experience with this first study it would seem important to (1) investigate a group of patients during the acute stage of illness; (2) study a group of nonparalytic poliomyelitis infections; (3) investigate further the cerebrospinal fluid findings during the acute stage of illness; and (4) determine the type of viruses that are causing illness in these areas. Such an investigation is already in progress.[14]

CONCLUSIONS

1. A report is made of a study of 100 patients during an outbreak of poliomyelitis that occurred in El Salvador, Central America, in 1953.

2. The symptoms, signs, cerebrospinal fluid findings and diagnoses are described.

3. The clinical differences are emphasized between poliomyelitis virus infection in the tropics and poliomyelitis virus infection in general in the temperate and arctic regions.

4. Clinical similarities are pointed out, however, between polio infection in general in the tropics and infection in a certain age group in the temperate areas.

5. On the basis of this similarity and the differences clinically and epidemiologically, two contrasting types of infection by poliomyelitis virus are distinguished.

6. The implications of these studies in the light of the history of poliomyelitis in general and the present status of poliomyelitis in the tropics in particular are discussed.

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OBSERVATIONS ON THE TREATMENT OF SCHISTOSOMIASIS MANSONI WITH FUADIN *

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In recent years there has been a considerable increase in the number of people of Puerto Rican birth living in New York City. By the end of 1953 this group had grown to 355,000 persons, nearly a doubling in size since 1950.[1] An anticipated medical result of this mass migration has been the recognition here among these people of many cases of chronic infection with the trematode worm, *Schistosoma mansoni*. In Puerto Rico, with a population of 2,250,000, the incidence of schistosomiasis is about 10%, and in some localities the infection rate exceeds 30%.[2] Fortunately, the specific snail vectors required for the transmission of this disease have not been found in the New York area nor in the other parts of the continental United States, and there is probably no danger that it will ever become endemic here.[3] However, physicians practicing in New York and in other new centers of Puerto Rican population should become acquainted with the medical features of schistosomiasis in order to deal intelligently with the clinical problems it presents. For an account of the epidemiologic, pathologic and clinical aspects of the infection, several excellent reviews may be consulted.[4, 5] It is the purpose of this report to present the results of a study of the treatment of the disease with antimony pyrocatechol sodium disulfonate (Fuadin, Stibophen).

Description of Clinical Material and Methods

Forty-six cases of chronic *Schistosoma mansoni* infection were studied on the medical and pediatric wards of the Mount Sinai Hospital. The group consisted of 39 males and seven females, who varied in age from 11 to 46 years. Eight of the patients were under 18. Twenty-six had lived in New York City less than five years; the others, for from five to 20 years. Fifteen of the patients had no complaints clearly referable to the infection. Thirty-one had classic symptoms of the disease, i.e., weakness, anorexia, epigastric pain and fullness, intermittent diarrhea and constipation. Palpable enlargement of the liver was detected in 43 (93%). The spleen was definitely palpable in only 20 (43%). The eight adolescent patients showed evidence of physical retardation.

The diagnosis was made by finding the lateral-spined ova of the parasite in stool specimens as a result of the microscopic examination of direct saline smears or of material obtained by centrifuging in a mixture of ether and

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concentrated hydrochloric acid, or by sedimentation in saline.[6] In most of the patients, other helminth ova and protozoan cysts and trophozoites were also found in the stools. A moderate eosinophilia (5 to 28%) was present in 90% of the cases. Two patients with severe anemia, leukopenia and marked hepatosplenomegaly were not included in the group to be reported on in this study.

The purpose of therapy was to prevent further damage to the tissues, chiefly the portal venous system, the liver and the colon, by the adult worms and the ova deposited by them.[7] Treatment was considered warranted only if viable ova were found in the stools or rectal biopsy specimens indicating active infection.[8] Twenty-two patients were given Fuadin (Stibophen) as follows: To 19 patients, 40 to 50 c.c. were administered by intramuscular injections within a 15 to 19 day period. One and one-half cubic centimeters, 3.5 c.c. and 5.0 c.c. were given on successive days, and then 5.0 c.c. on alternate days until the total amount had been given. Three of the younger patients were given 30 or 35 c.c. in the same period.

In an attempt to increase the effectiveness of the drug and to shorten the time required for treatment, 24 patients were given 19 to 57 c.c. of Fuadin (Stibophen) in five days. In each case the total dose was determined by the patient's weight and the following schedule: 10 received 1 c.c. per kilogram; seven, 0.75 c.c. per kilogram; seven, 0.5 c.c. per kilogram. As a rule two injections of 2.5 c.c. were given on the first day, two of 5.0 c.c. on the second and the third days, and then two or three doses of 5.0 c.c. daily on the fourth and fifth days until the total had been given. Upon the completion of therapy, as many of the patients as would coöperate were observed at monthly intervals in the Tropical Disease Clinic of the Outpatient Department of the hospital. Since the adult worms may require several months to recover from the effects of inadequate therapy, the criterion of cure was the continued absence of viable ova from stool specimens concentrated for examination and from biopsied specimens of rectal mucosa for the year following therapy.[7, 8]

The antimony pyrocatechol sodium disulfonate (Fuadin, Stibophen) was supplied in ampules containing 5.0 c.c. Each cubic centimeter contained 63 mg. of the drug. The trivalent antimony content was given as 8.5 mg. (13.6%).[9]

Results

In the group of 22 patients treated by the long method, 16 (72%) had stools that were negative for schistosoma ova immediately after treatment. In the six other cases, ova were readily found. Thirteen of the former were followed for from two to 12 months, and viable ova reappeared in the stools in seven (54%). Four had negative stools for from eight to 12 months. Thus, 13 (60%) failed to respond to a single course of therapy. Second courses were given to four of these patients and were also ineffective.

In the group treated for five days, upon completion of therapy negative

stools were obtained in 23 (96%). Among 19 followed for from three to 12 months, in six viable ova reappeared in the stools. The total number of known failures was seven (27%), and the number of apparent cures was increased to eight (33%). Treatment was most effective in the patients who had received the largest amounts of Fuadin (Stibophen). In the group treated with 1.0 c.c. per kilogram there were no known relapses among the seven we were able to follow. Four were observed for one year, two for eight months and one for three months. Of seven treated with 0.75 c.c. per kilogram, one failed to show even a temporary response to the drug, and two relapsed within three months. A fourth had had negative stools for four months when he failed to return for further study, and three for 12 months. Among the five patients given 0.5 c.c. per kilogram, four relapses were noted within three months. The fifth had negative stools for one year and was considered cured.

It was our impression that treatment was associated with improvement in the general health of these patients. Many who had been subject to abdominal distress prior to therapy stated that they felt considerably relieved after it. Increase in weight and an acceleration of growth were noted in most of the adolescent patients after treatment. The palpable enlargement of the liver and spleen present prior to therapy usually remained unchanged during the follow-up period.

Untoward Reactions to Treatment

Treatment was well tolerated by the patients who received the long course. Slight nausea, anorexia and mild upper abdominal pain were complained of in half of the group. Two developed elevations in temperature (100 to 101° F.) and tenderness over the liver area during therapy. In 15 a decrease in the amplitude or slight inversion of the T wave in some of the leads of the electrocardiogram was observed during the second week of the treatment.[10] These changes returned to normal in two or three weeks. The only notable hematologic finding was an increase in the percentage of eosinophils in the blood in two patients.

Among the patients given Fuadin (Stibophen) in five days, reactions were common and severe. This was especially true of the 17 cases to whom the largest amounts were administered. The symptoms and signs of toxicity usually appeared on the fourth or fifth days. Seventeen patients complained of severe nausea which lasted for from 24 to 96 hours. Vomiting and cramplike upper abdominal pain were also noted in 12. Temperature elevations to 101 to 102° F. were present in eight. Five developed maculopapular erythematous rashes on the face, chest and extremities. In one, the rash was described as urticarial and appeared several days after treatment had been completed. In a boy of 12, treatment was followed by the appearance of a syndrome of fever, migratory polyarthritis, pulmonary infiltrations and marked eosinophilia (70%) that lasted for eight days. Pain

and stiffness of the joints of the extremities and fever were noted in three other patients.

In 10 of these 17 cases there was a temporary increase in the percentage of eosinophils in the peripheral blood after treatment, and in two a leukocytosis was noted also. In two, retention of sulfobromophthalein sodium (Bromsulphalein) was observed as a result of therapy, i.e., the level rose from 10% to 23% and from 4% to 26%, respectively. The excretion of the dye was normal two weeks later. Electrocardiographic changes were noted in all of the cases and consisted of varying degrees of inversion of the T waves, which usually persisted for two or three weeks.

Treatment of Fuadin Toxicity with Dimercaprol (BAL)

In an attempt to ameliorate the toxic effects of Fuadin (Stibophen), Dimercaprol (BAL) was administered to three cases who developed severe reactions. The first case, a 19 year old girl, developed intense nausea, repeated episodes of vomiting, an erythematous generalized punctate skin eruption and a fever (101° F.) on the fifth day of therapy. Shortly thereafter she had a series of generalized convulsions in rapid succession, and a tachycardia of 130 beats per minute was noted. An electrocardiogram revealed the presence of sinus tachycardia and inversion of the T waves in the standard and precordial leads (V leads). She was treated with 1.5 c.c. of a 10% solution of Dimercaprol in oil intramuscularly every four hours for 24 hours. The convulsions ceased promptly, and improvement in her general condition, as evidenced by the relief of nausea and vomiting, was apparent within 12 hours after Dimercaprol was started. Although the tachycardia subsided in 24 hours, the T wave changes persisted for three weeks.

The second case, a young woman of 23, developed severe nausea, upper abdominal pain and vomiting on the fifth day of therapy. An electrocardiogram showed inversion of the T waves in all the leads. She was given 1.5 c.c. of Dimercaprol in oil intramuscularly every four hours for 24 hours. The use of the drug seemed to intensify her nausea and caused a burning sensation about the nose and eyes. Further inversion of the T waves of the electrocardiogram was noted during the 48 hours following the commencement of the Dimercaprol therapy. The tracing did not return to normal until 17 days after completion of Fuadin therapy.

The third case, a boy of 16, developed upper abdominal cramps, nausea and vomiting and a punctate erythematous skin eruption on the face, chest and arms on the fifth day of treatment. He was given 2.4 c.c. of Dimercaprol in oil every four hours intramuscularly until a total of 14.4 c.c. had been administered. Twelve hours after this drug was started his symptoms had almost completely subsided and did not recur. The use of the Dimercaprol produced no alteration in the inverted T waves of the electrocardiogram that developed on the third day of Fuadin therapy and persisted for three weeks.

Comment

Trivalent antimony compounds have been used in the treatment of the various forms of schistosomiasis since Christopherson reported the value of potassium antimony tartrate (tartar emetic) in infections with *Schistosoma haematobium* in 1918.[11] Although this drug has come to be regarded as the most potent therapeutic agent available for schistosomiasis, its use has many disadvantages. It has to be given intravenously, a drawback in treating native populations in endemic areas lacking trained medical personnel. The solutions of the drug have to be freshly prepared prior to its use; being unstable, they cannot be autoclaved; they are very irritating to the veins and perivenous tissues, and cause phlebitis and painful sloughs. Toxic reactions—i.e., coughing, nausea, vomiting, dizziness, epigastric pain, diarrhea, fever and painful stiff joints—have been common during therapy.[12] Sudden death has been observed following its administration.[13] A mortality rate of 0.5% was reported among 1,000 cases treated with the drug.[14]

In 1929, Khalil and his associates introduced antimony pyrocatechol sodium disulfonate (Fuadin, Stibophen) for the treatment of *S. haematobium* and *S. mansoni* infections.[15] Basing their conclusions largely on their experience with cases of infection with *S. haematobium,* they reported that this drug was more effective and less toxic than tartar emetic. Moreover, solutions possessed the advantages of availability in ampules, of chemical stability, of having little or no local irritant effect, and of ease of administration by intramuscular injection. They recommended the treatment of adults with 40 to 50 c.c. given in nine or 10 intramuscular injections within a period of 15 or 17 days. This regimen was used by us in the treatment of 22 of our cases.

Subsequent experience with this antimonial indicated that the dosage recommended by Khalil was usually inadequate for successful treatment.[7] Moreover, following its use toxic reactions were by no means uncommon, and a mortality rate of 0.2% was encountered.[12] It was found that infections with *S. mansoni* and *S. japonicum* were generally more resistant to treatment with it than were infections with *S. haematobium.* In cases of infections with *S. mansoni* in Puerto Rico, the relapse rate following a single course of therapy exceeded 50%, and several courses had to be given in order to eradicate the parasites.[16] Similar experiences were reported with cases of *S. japonicum* infection in the Far East, where it was necessary to increase individual doses and the length of the period of treatment.[12] Recently, a committee of the World Health Organization, in a report on the present status of the problem of schistosomiasis, rated Fuadin as 45 to 65% efficient in the treatment of this disease, and stated that its intramuscular use was justified only in small children and at treatment centers lacking a skilled staff.[18]

Several reports have indicated that it is possible to increase the therapeutic value of Fuadin (Stibophen) by intensifying treatment, i.e., by in-

creasing the size of single doses, by shortening the time intervals between their administration, or by extending the series of injections. Mason et al. observed a relapse rate of 80% in patients with *S. japonicum* infections treated with 65 c.c. of the drug (.57 gm. of antimony) in 25 days.[19] In contrast, the same amount of antimony (.58 gm.) given as tartar emetic in 29 days cured 81% of the patients. In studies of the treatment of *S. japonicum* infections by Most and his collaborators, a relapse rate of 79% was obtained in 43 patients after administration of 70 c.c. of Fuadin in 27 days.[20] The relapse rate fell to 60% in 64 patients given 100 c.c. in 14 days. In 28 patients with *S. mansoni* infections given 70 c.c. in 27 days there were no relapses in four months. Most observed a low relapse rate in a series of several hundred cases of infection with *S. mansoni* given 100 c.c. of Fuadin in daily doses of 5.0 c.c.[21]

Our study confirms the reported observations that a single course of 40 to 50 c.c. of Fuadin (Stibophen) administered over a period of 15 to 19 days is usually inadequate for the cure of *S. mansoni*. On the other hand, the administration of comparable amounts in five days reduced the number of relapses. Our data suggested that a dose of 1.0 c.c. per kilogram of body weight given in five days was capable of killing the adult worms, since there were no known failures in a small group so treated. Despite the shortened treatment period, three quarters and one-half of this dose were less effective. The intensive use of Fuadin was attended by a high incidence of untoward effects, indicating that the five day schedule is not safe for clinical use. These findings seem to be in keeping with the results of in vitro studies, which have shown that Fuadin killed adult schistosomes only at high concentrations.[22, 23]

The latent period prior to the development of Fuadin toxicity observed in our cases was noted also by Rose and was due most likely to the accumulation of the drug in the body.[24] Brady et al. showed that there was a continuous accumulation of radioactive trivalent antimony, chiefly within the liver and thyroid gland, after multiple daily injections in the dog.[25] According to Khalil, the excretion of Fuadin takes place slowly after injection and occurs mainly through the kidneys. Since there was no clear-cut relationship between the dose of Fuadin and the occurrence of toxicity, he concluded that variations in tolerance may depend on the adequacy of the renal excretion of the drug.[26]

The occurrence of an increase in eosinophilia following therapy, noted in 12 of our cases, has been observed by others. Pessoa and Coutinho reported an increase in eosinophilia after the treatment of schistosomiasis with Fuadin, and regarded this as an indication of the therapeutic potency of the drug.[27] Lyons and Benson observed an absolute eosinophilia in 20% of 26 cases of *S. mansoni* infection, and concluded also that this was an indication of the efficiency of treatment.[28] In our series, post-treatment eosinophilia was noted in nine patients whom we considered cured by therapy and in only three patients who were unsuccessfully treated. It is our belief that this

eosinophilic response is a reaction to the killing of the worms and is a sign of effective therapy.

It has been postulated that the lethal action of Fuadin (Stibophen) on adult schistosomes is due to an interference with sulfhydryl enzymes, since the inhibitory effects on glycolysis can be reversed by Dimercaprol.[22, 23] The value of the latter drug in the treatment of arsenic, gold and mercury poisoning is generally accepted.[29] However, the results in antimony poisoning have been regarded as inconclusive. Rittey reported the successful use of Dimercaprol in one case of acute antimony dermatitis.[30] In three cases of Fuadin toxicity treated by us with short courses of Dimercaprol (9 to 14.4 c.c. in 24 hours), the drug seemed of value in two, since its use was associated with termination of a convulsive state and symptomatic improvement. In none of these cases was there any notable effect by Dimercaprol on the intensity and persistence of the electrocardiographic changes (T wave inversions) induced by Fuadin.

Summary

1. The administration of 40 to 50 c.c. of antimony pyrocatechol sodium sulfate (Fuadin) in 15 to 19 days to 22 patients with *S. mansoni* infection resulted in a treatment failure rate of 60%.

2. The number of unsuccessful treatments was reduced to 28% among 24 cases given 19 to 57 c.c. of the drug in five days.

3. The best therapeutic results were obtained in a group of patients who received the largest amounts of Fuadin (1 c.c. per kilogram) in five days.

4. The incidence of serious toxicity from Fuadin was high among the patients treated in five days, and this procedure is regarded as unsafe.

5. The administration of Dimercaprol (BAL) seemed to be of clinical value in two cases of severe Fuadin intoxication. This drug had no detectable effect on the electrocardiographic changes produced by Fuadin in three cases.

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BACTERIAL ENDOCARDITIS IN THE AGED*

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FOR many years the occurrence of bacterial endocarditis in the older age group has been inadequately emphasized. A review of several groups of patients with bacterial endocarditis reported in the literature indicates that a considerable number of these cases occur in older patients. These figures appear in table 1.

In 1940 Bayles and Lewis [4] reviewed 28 cases in patients more than 40 years of age in whom the diagnosis was established at autopsy. They observed that subacute bacterial endocarditis had "not been sufficiently considered in those over 40." Sixteen (57%) of their cases were superimposed on rheumatic heart disease, seven (25%) on arteriosclerotic heart disease, two (7%) on luetic heart disease, and three (11%) on bicuspid aortic valves. These authors concluded that "the clinical features are essentially the same as those in younger patients, but less accentuated. Congestive heart failure and azotemia are more common; demonstrable bacteremia is less common. Subacute bacterial endocarditis occurs more frequently than suspected or heretofore reported in older individuals."

In 1940 Willius [12] reported a case of an 82 year old man with subacute bacterial endocarditis. (This case was not autopsied.) He pointed out that "in the vast majority of cases the patients are less than 50 years of age."

Zeman and Siegal [13] reviewed the literature and reported nine cases of acute bacterial endocarditis and 18 cases of subacute bacterial endocarditis in patients over the age of 60. They emphasized the significance of acute endocarditis in the aged because of the increasing proportion of older people in the population as well as the promising effect of therapy. Of their nine cases, four had had rheumatic heart disease, one arteriosclerotic thickening of the valve, and four had had no previous valvular damage of any kind. These authors stated that "acute bacterial endocarditis may complicate any infectious disease in old people. It is to be considered as a diagnostic possibility in any febrile condition of the aged which is associated with bacteremia, and the more so if there is no response to specific therapy." They further stated that "the course of the acute type of endocarditis is fulminating and often diagnostically obscured by reason of the prostration of the patient, which tends to mask the symptoms." They noted that the subacute variety presents greater diagnostic difficulties in old people, but is correctly diag-

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TABLE 1

Distribution by Decades of Several Reported Series of Patients with Bacterial Endocarditis

Author	Total Cases	0–9	9–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	% of Cases Over Age 50	Comment
Blumer[1]	317	1	54	116	86	37	19	4	0	0	7%	Clinical cases—294 from literature
Davis and Weiss[2]	47	0	2	8	12	18	4	2	1	0	15%	*†
Hedley[3]	118	7	18	37	25	13	15	3	—	—	15%	†
Bayles and Lewis[4]	42	0	2	4	8	7	14	5	2	0	50%	*† Patients under 12 not included
Christian[5]	150	0	10	56	10	25	28	15	5	1	33%	* Patients under 12 not included
Denman[6]	50	6	3	9	17	10	5	0	0	0	?	† Excluded 6 cases over 59 "because of their age"
Gelfman[7]	115	4	13	28	15	26	21	5	2	1	25%	†
Kelson and White[8]	250	6	42	78	55	40	20	8	2	0	12%	* Clinical cases
McDonald[9]	196	6	20	53	41	32	28	10	3	3	22%	†
Clawson[10]	417	8	38	91	98	79	56	36	8	3	25%	†
Correll et al.[11]	70	1	5	12	19	13	13	7	—	—	28%	Clinical cases—48 studied at autopsy
Wallach, Lukash and Angrist	I—82	0	13	18	21	17	5	5	3	0	16%	†
	II—47	5	4	4	8	9	7	6	2	2	36%	

* = Approximate numbers from charts. † = All studied at autopsy.

nosed more often because these patients are under observation for a longer period of time.

In Zeman's [14] report of 18 older patients with subacute bacterial endocarditis (14 of whom were autopsied), he classified nine as presenting the typical, though often modified, clinical picture. The rest of these patients presented serious diagnostic difficulties: five were bacteria-free cases, and in four more the diagnosis was completely obscure. Zeman stressed the diagnostic difficulties, some of which he attributed to the presence of the numerous other diseases so frequently present in the older age group. He again pointed out that subacute bacterial endocarditis occurred in the aged more frequently than is generally realized, and that an increased incidence may be expected with the increasing number of old people in the general population.

In 1949 Traut et al.[15] reported 94 autopsied cases of bacterial endocarditis in patients over 45 years of age; these occurred among 13,661 autopsies at Cook County Hospital from 1935 to 1946. Of the 94 cases, 67 showed rheumatic involvement, five had arteriosclerotic heart disease, 12 had aortic syphilis, and two had congenital defects. In 18 cases no antecedent heart diseases were found, and this was particularly common in the ulcerative group. These authors concluded that active endocarditis seldom if ever occurs in a normal heart, and that bacterial endocarditis commonly occurs in the elderly patient.

Monroe [16] found 18 cases of bacterial endocarditis (nine acute, nine subacute) in 332 cases of valvular heart disease in 7,941 patients more than 61 years of age studied clinically and pathologically. In addition, he summarized 10 patients with vegetative endocarditis in normal hearts with no

evidence of rheumatic disease or congenital defects. Two cases were nonbacterial, two were subacute, eight were acute; nine were men and one was a woman.

Sprague and Carmichael [17] noted acute bacterial endocarditis in 11 patients (eight with previous rheumatic damage), and subacute bacterial endocarditis in seven patients (six with previous rheumatic damage). These occurred in 1,025 autopsied cases over age 49.

Material and Methods

As part of a larger study, a series of 8,676 consecutive autopsies performed at the Queens General Hospital from 1936 to 1950, inclusive, was reviewed.[18] Five hundred and nine (5.9%) of these were classified as rheumatic heart disease because they fulfilled the following criteria: (1) fusion and retraction of the mitral or tricuspid valves; (2) fusion and shortening of the chordae tendineae; (3) noncalcific fusion of the aortic valve; (4) any fusion, including calcific changes, of the aortic valve when it was associated with definite rheumatic mitral valve involvement; (5) active rheumatic heart disease with Aschoff's bodies or characteristic verrucae; (6) bacterial endocarditis of the mitral or aortic valves with some evident previous distortion, the exact estimation of the severity of rheumatic damage being difficult. Cases showing the following changes were excluded from the rheumatic category: (1) slight mitral changes (for example, tonguelike extensions of the valve cusps), or distortion which did not fulfill the criteria stated above (points 1 and 2); (2) slight aortic stenosis, with or without slight mitral involvement; (3) calcific aortic stenosis, with or without mitral

Table 2

Summary of 13 Cases in Group I
(with Underlying Rheumatic Heart Disease)

Case No.	Age	Color	Sex	Heart Weight	Severity of Rheumatic Valvular Lesions*	Nature and Location of Bacterial Vegetation*	Bacteria Recovered
1	53	W	F	320	M 2+, A 2+, T 1+	s-M	Viridans
2	56	W	M	500	M 4+, A 4+	a-M	Nonhem. strep. *B. coli*
3	51	W	M	520	M 2+, A 2+	a-A & M	Hem. staph.
4	57	W	M	520	M 3+, A 2+	s-M	
5	57	W	M	420	M 2-3+	s-M	Viridans
6	61	W	M	420	M 3+, A 2+	a-M	Aerobacter
7	65	W	F	380	M 4+, T 3+ A & P 1+	a-M	
8	60	W	M	430	A ? (destroyed), M 2+	s-A	Viridans
9	63	N	M	870	M 3+, A 2+, T 1+	s-A, ? M	
10	69	W	M	450	M 2+	a-M, MacCal	
11	75	W	F	460	M 2+, A 4+	s-A	Viridans
12	72	W	F	390	M 3+	a-A	Hem. strep.
13	72	W	M	500	M 3+	a-M & LA	Hem. strep.

* A = Aortic. M = Mitral. T = Tricuspid. P = Pulmonic. MacCal = MacCallum's site. a = acute bacterial endocarditis, s = subacute bacterial endocarditis.

TABLE 3
Summary of 17 Cases in Group II
(Do not Meet the Criteria for Rheumatic Heart Disease)

Case No.	Age	Color	Sex	Heart Weight	Nature and Location of Bacterial Vegetation*	Bacteria Recovered
1	58	W	M	670	s-A	*Strep. viridans*
2	52	W	M	350	a-A	Pneumo. V
3	58	W	M	380	a-M & A	Pneumo. I
4	53	W	M	?	a-M	Nonhemol. staph.
5	51	W	F	350	a-A & M	*Staph. aureus*
6	57	W	M	400	a-M	
7	59	?	F	500	a-M	Hemol. strep.
8	63	W	M	400	a-M, T	
9	61	W	M	530	a-A	
10	66	W	M	400	a-M	Hemol. strep.
11	61	W	F	290	s-M	Nonhemol. *Strep. viridans*
12	64	W	M	380	a-T, A	*Strep. viridans*, hemol. strep.
13	60	W	M	420	a-A, T	Pneumo. V
14	72	W	M	370	a-M	Staph., pneumo. XVIII
15	74	W	M	360	a-M & A	
16	81	?	M	400	a-M	
17	86	W	M	400	a-M	

*A = Aortic. M = Mitral. T = Tricuspid. P = Pulmonic. a = acute bacterial endocarditis, s = subacute bacterial endocarditis.

changes; (4) calcification of the valve rings alone. Thus, 103 cases of calcific aortic stenosis and 72 cases of doubtful origin were excluded from this study.

The severity of the rheumatic valvular stenosis was graded from 1 to 4 plus, 1 plus being the least severe involvement, yet sufficient to meet the criteria above, and 4 plus being the most severe involvement and representing valves described as "fish-mouth," "button-hole," "slitlike," "markedly stenotic," "could not admit one finger." Two and 3 plus represented the intermediate degrees of severity.

Bacterial endocarditis was present in 82 (16.1%) of the 509 patients with rheumatic heart disease (Group I), and in an additional 47 cases in whom the hearts did not meet these criteria for rheumatic heart disease (Group II). Thirteen patients in Group I and 17 patients in Group II were more than 50 years of age and form the basis of this report. These patients are summarized in tables 2 and 3.

RESULTS

Of 82 cases of bacterial endocarditis with underlying rheumatic heart disease (Group I), 13 were in the older age group, and the endocarditis was acute in seven of these. The endocarditis was acute in only 14 of 69 younger patients. In contrast, 47 instances of bacterial endocarditis without underlying rheumatic heart disease (Group II) included 17 examples in the aged; 13 of these were acute.

The older patients with acute endocarditis more frequently evidenced genitourinary infection, diabetes, bronchopneumonia (probably secondary),

postoperative status, and sclerotic changes in valves. The acute disease in the younger patients was more often associated with lobar pneumonia, meningitis, postabortal status, and status following dental manipulation; the underlying heart disease, when not rheumatic, was usually luetic aortitis, lupus erythematosus or congenital heart disease. Significant differences between younger and older patients are summarized in table 4. Most of these cases occurred prior to the time of extensive use of chemotherapy, but a few occurred more recently.

In the younger age group *Streptococcus viridans* was the etiologic agent in seven of 30 cases without rheumatic valvular involvement, and in 33 of 38 cases with rheumatic valve distortion. This compares with four of 13 older cases in Group I and three of 17 older patients in Group II.

TABLE 4

Comparison of Endocarditis in Older and Younger Patients

Older Patients	Younger Patients
1. Usually incidental terminal event	Usually the mechanism of illness and death
2. Postoperative status	Postabortal status, postdental manipulation
3. Associated illness: genitourinary infection, bronchopneumonia (probably secondary), diabetes, malnutrition	Associated illness: primary infections, e.g., meningitis, lobar pneumonia
4. Often septic organisms	More often *Str. viridans*
5. Often acute ulcerative valvulitis	More often subacute vegetative endocarditis
*6. Sclerotic changes in valves	Luetic aortitis, lupus erythematosus, congenital heart disease
†7. Fewer glomerular lesions	Glomerular lesions more frequent

* This comparison obviously is applied particularly to patients in Group II without underlying rheumatic heart disease.

† Applies particularly to patients in Group I.

Although it is frequently difficult to decide the cause of death in patients with multiple lesions, it is our impression that in older patients the endocarditis often represents only an incidental terminal infection of a fresh nonbacterial thrombotic vegetation, and actually plays little real part in the basic primary mechanism of death of the patient. It is a terminating event. In contrast, in the younger patients, particularly in Group I, the bacterial endocarditis was usually directly and immediately responsible for the illness and the death of the patient.

An additional finding of interest was the higher incidence of glomerular lesions, particularly in patients under 50 years of age. In Group I these lesions, including chronic and acute diffuse and focal embolic glomerular nephritis, occurred in 33 of the 82 cases; only four of these were in the older group. Group II included only a few instances of such glomerular lesions.

COMMENT

The results show that a larger proportion of older patients with bacterial endocarditis develop this lesion in the absence of underlying rheumatic heart

disease. Thirteen of the 30 cases (43%) in the older age group met the stipulated criteria for rheumatic valves. This compares with the figures of 57% and 71% in other series.[4, 15] This variable incidence undoubtedly reflects the difficulty in diagnosis and the individual criteria used in classifying valves as rheumatic. It is our opinion that many distorted valves in the aged are classified as rheumatic on the basis of nonspecific sclerotic changes.[18h]

In these older patients the endocarditis is more often of the acute type. This is true on the basis of pathologic criteria for acute endocarditis as well as duration. More of these cases of endocarditis are of the ulcerative rather than the vegetative variety. Fewer of the cases are due to *Streptococcus viridans,* and many such valves, whether or not infected with *Streptococcus viridans,* lack the morphologic criteria of subacute bacterial endocarditis, approaching the acute picture pathologically. More often the bacteriology includes a wide range of septic organisms.

The higher incidence of glomerular lesions in Group I, particularly in patients under 50 years of age, may have several explanations. It may be an expression of the known association of rheumatic fever with vascular lesions in general, and with lesions of the vascular glomerular tufts in particular. Furthermore, in the patients with underlying rheumatic heart disease (Group I) the duration of the bacterial endocarditis is more often longer than in the cases in Group II without underlying rheumatic heart disease, in whom the bacterial endocarditis was more often acute and was so often a terminating event. This longer duration of a bacteremia allows for sufficient time to develop the glomerular lesions, and the very nature of the responsible bacteria in this group (e.g., *Str. viridans*) is more often associated with sensitivity phenomena than are the bacteria usually responsible for the more acute endocarditis. Conversely, the more septic bacteria seen in acute bacterial endocarditis go with a poor prognosis and shorter illness before death or complete recovery. Another factor may be the depression of sensitivity and inflammatory phenomena in the debilitated patient subject to a severe terminal infection. It is most probable that a balance or summation of several of these factors is responsible for the different incidence of glomerular lesions in the two groups of patients. All in all, there is less time as well as a diminished tendency on grounds of immunity and reactivity for the development of glomerular lesions.

The pathogenesis of bacterial endocarditis has been demonstrated to represent infection of nonbacterial thrombotic lesions on the valves.[19, 20] This nonbacterial thrombotic lesion tends to occur in or on valves whose collagen has become dense and fibrous. The most common predisposing cause of this collagen change, particularly in younger patients, is rheumatic valvulitis. However, with increasing age the degenerative changes of senility and other degenerative diseases play a more important rôle, thus accounting for the more frequent failure to find an underlying rheumatic, luetic or congenital lesion in aged patients. Even in the presence of original

rheumatic alterations it is the superimposed nonspecific sclerotic changes which are often more significant. The metabolic defect of the aging process in the collagen makes the valves particularly susceptible to stress (e.g., infection, operation, injury, diabetes), and this favors the formation of the nonbacterial thrombotic vegetation. The associated breakdown of immunity favors blood stream invasion by infecting organisms. The more frequent contamination of such nonbacterial thrombotic vegetations is to be expected, and the bacterial endocarditis is thus established. Prolonged stress in the moribund patient may well be responsible for the increased incidence of the terminal vegetations found so much more often in the aged. The diminishing frequency of rheumatic and luetic heart disease and the earlier discovery and treatment of congenital cardiac lesions will decrease the proportion of these cases with bacterial endocarditis superimposed. The absence of the characteristic murmurs and of the helpful antecedent history of rheumatic heart disease will make the diagnosis of bacterial endocarditis more difficult. The increasing number of older people in the population will also further increase the proportion of cases of bacterial endocarditis superimposed on senile alterations in the collagen. The presence of numerous more dramatic diseases demanding attention in this age group may confuse the clinical picture. The use of inadequate doses of chemotherapy or the selection of the improper antibiotic agent, with the opportunity for the evolution of resistant organisms, the lowered resistance and immunity reaction generally, as well as the failure to suspect active bacterial endocarditis in the aged, represents additional significant hazards for the older patient with bacterial endocarditis.

Summary and Conclusions

Bacterial endocarditis occurred in 82 (16.1%) of 509 autopsied patients with rheumatic heart disease (Group I); these patients were compared to an additional 47 cases in whom the hearts did not meet the criteria for underlying rheumatic heart disease (Group II). The patients more than 50 years of age in each group were analyzed and compared with the younger groups of patients.

The differences in the type of antecedent infection, the preceding valvular alteration, the frequency of glomerular lesions and the rôle of bacterial endocarditis in the death of the patient are noted, and the explanation and significance of these findings are discussed.

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THE "DOVE-COO" MURMUR AND MURMURS HEARD AT A DISTANCE FROM THE CHEST WALL *

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AMONG all sounds emanating from the human heart, the "dove-coo" or "sea-gull" murmur is unique. None so closely approximates a pure musical tone, and none is so clearly perceived by the ear. Its flowing note, characteristically decrescendo and sliding downward in pitch as it is prolonged throughout most of diastole, bears a startling resemblance to the coo of a dove. Variously described as the "sea-gull cry," the "humming top" or "whistling" murmur, it is referred to in most cardiology textbooks simply as the musical murmur of aortic regurgitation. Its differentiation from ordinary murmurs, which may occasionally possess some degree of "musical quality," is usually quite obvious on auscultation, enabling one to recognize it readily as a specific type of heart murmur.

A frequently observed characteristic of the dove-coo sound is its often phenomenal degree of audibility. It may be heard over the entire trunk and even in such remote anatomic sites as the top of the head and the extremities. Generally the midprecordium is the area of maximal intensity. Of all murmurs, this is the one most frequently described as being audible without a stethoscope, at distances of from a few inches to several feet from the chest wall. In fact, the patient himself may become aware of a strange sound in his chest and may complain of its unremitting annoyance.

Although some of the earlier descriptions of musical murmurs are difficult to identify with certainty, probably several hundred cases of the "dove-coo" type have been recorded in medical literature over the last century and a half. A few articles have appeared in the American literature of recent years emphasizing the pathologic findings in 50 or so cases. As a result, the "dove-coo" murmur is now more than an interesting curiosity; it is becoming recognized as an auscultatory finding of considerable clinical significance.

The exact nature of this peculiar murmur has been a subject of special interest to us in our studies of heart sounds. This presentation is primarily concerned with an approach to the problem through an investigation of the

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The electronic heart sound pickup, described in previous papers,[11, 12] was developed in collaboration with the General Motors Research Laboratories, Detroit, Michigan, as a contribution of the General Motors Corporation to cardiovascular research.

sound itself. Present day electronic technics afford an opportunity for objective study of such sounds recorded graphically from the precordium.

Previous Studies, Clinical and Pathologic

The first observation of loud musical diastolic murmurs is probably lost in antiquity. Interest in heart sounds became widespread following Laennec's invention of the stethoscope in 1819, and Laennec [1] himself may have observed the phenomenon when he wrote of ". . . more than twenty subjects in whom I have heard the pulsation at a distance of from two inches to two feet. . . ." Hodgkin in 1829, and perhaps Key in 1827, are reported [2] to have attributed the "bruit de scie," likened to the "cooing of a dove," to retroversion of an aortic valve leaflet.

Hope [3] wrote of some 14 cases observed by him during the 1830's, describing the murmur as "like whistling, cooing, or the mewing of a kitten." In one patient who came to him complaining of a noise in the chest he found the noise to be "a musical note, audible at the distance of no less than two feet." It was Hope who noted that the peculiar murmur was "most apt to result from regurgitation," and that "presentation of an edge to a stream is best calculated . . . to produce musical vibrations." He adds in his book an interesting speculation on genesis of the sound: ". . . in reference to musical murmurs of the valves of the heart, . . . there is but a shade of difference in the mechanism by which we make the lips produce a blow or a whistle, the latter depending on the happy and steady adaptation of the size of the aperture to the strength of the current."

Other causes for the musical sound have been suggested from time to time—vegetations on valves, calcification of a leaflet or valve orifice, anemia, anomalous vibrating cords within the ventricle, dilatation of the aorta, and damage or rupture of valve cusps by trauma, war gas or infection. Usually the aortic but sometimes the mitral valve has been identified as the site of origin. Syphilis and rheumatic fever have received most frequent mention as underlying etiologic factors. One author (Hanns) [4] disclaimed anatomic lesions altogether as a cause, advancing the explanation that musical murmurs depend entirely on tachycardia and are produced by equalization of pressures on the two faces of a vibrating body.

Certainly not all musical murmurs are of the "dove-coo" type, nor are they of pathologic significance. Many of those described in children and young patients may represent venous hums, as judged by their transitory nature, their alteration with changes in posture, and their localization in the supraclavicular area. Those which do have a musical character tend to be more continuous, with the pitch of the tone sliding up and then down, rather than the recurrent descending "coo." Murmurs of the up-and-down type, doubtless of more common occurrence, were described by Laennec,[1] who observed that "occasionally they compose a certain succession of musical tones, as if the artery were become a vibrating string, from which two or

three notes were drawn out in succession, by advancing and drawing back the finger upon it." Some of these have likewise been reported [8] as audible without a stethoscope.

Undoubtedly other types of murmurs are occasionally heard at a distance from the chest wall. It is noteworthy that, almost without exception, they have been described as having a musical quality. Sir William Osler reported [5] in 1880 one such case, that of an apparently normal girl of 12 who, only at certain unpredictable times, emitted a loud systolic murmur which "was distinctly audible at a distance of three feet two inches by measurement, and could be heard at any point on the chest and on top of the head." In the same report Osler mentioned two of his cases of aortic stenosis in whom a systolic murmur was "audible at about three inches from the sternum." The same observation has been reported more recently in aortic stenosis,[6] and also in a case of mitral stenosis.[7] In the latter "a harsh, . . . partly rough, partly musical" systolic murmur was heard, and "at every heart beat a clicking or slightly sonorous sound was audible in the room," the main frequency of which was estimated to be 230 to 250 cycles per second.

There is of course another group of sounds, synchronous with heart action and dependent upon the presence of air within the heart for their production (the "mill-wheel" murmur), or on abnormal combinations of air and fluid in the pericardial or pleural spaces. A comprehensive review of such bizarre sounds was recently published by Bean.[8] In general, they are described as "churning," "clicking" or "splashing" noises which, by their nature, may be considered to be of considerably higher frequency (pitch) than ordinary heart murmurs.

Pathologic studies of cases manifesting musical diastolic murmurs of the "dove-coo" or "sea-gull" type have shown most of them to be associated with eversion or retroversion of an aortic valve cusp,[2] usually from syphilitic aortitis. In these the life expectancy is short and, owing to the abrupt increase in the load on the left ventricle, congestive failure often appears concurrently with onset of the musical murmur. Autopsy studies have shown rupture, or perforation, of an aortic cusp [9] to be an occasional finding. Rheumatic and subacute bacterial endocarditis are said to be less frequent causes of the valvular deformity, about two thirds of 48 reported cases being of syphilitic etiology. Emphasis has been placed on the observation that it is the right anterior aortic valve cusp which is usually involved,[10] thus depriving the right coronary artery of its valve shelf and jeopardizing the coronary circulation. The grave prognostic significance of the "dove-coo" murmur is illustrated by a recent series [10] of 10 cases, all of luetic etiology, in which nine of the patients died within nine months of discovery of the murmur, the remaining case surviving 18 months. Gelfand and Bellet [9] made phonocardiographic recordings from several of their patients and found the murmurs to have a frequency, in vibrations per second, of 130 to 340 at onset, decreasing to their lowest pitch of 90 to 210 in presystole. They also

stressed the generally poor prognosis denoted by the murmur, and the adverse effect on circulatory dynamics produced by the associated abrupt increase in degree of aortic valve insufficiency.

The Present Investigation

Methods for depicting heart sounds graphically are not new. The conventional phonocardiogram is one such method, but one which, in its present form, is not ordinarily expected to depict the wave form and component frequencies of recorded sounds in detail, due chiefly to limitations in its microphone pickup and galvanometer oscillograph.

A calibrated electronic type of heart sound pickup for use in direct contact with the chest wall has recently been developed in collaboration with the General Motors Research Laboratories.[11] This pickup was designed primarily for low (subaudible) frequency vibrations, but is capable of reproduction of sounds up to 500 c.p.s. Used in conjunction with a cathode ray oscilloscope and camera, it records the wave form of heart sounds and murmurs in considerable detail.[12] This technic of electronic reproduction was employed in study of the dove-coo murmurs of the following two cases:

Case Reports

Case 1. A 53 year old colored male was admitted to the Medical College of South Carolina Heart Clinic in December, 1953, complaining of shortness of breath. He dated his symptoms to two months previously when, while at work as a railroad laborer, he noted a "pounding" sensation in the chest, followed by dyspnea on exertion and orthopnea of increasing severity, rendering him unable to continue work. Since onset of his illness he had become aware of a peculiar whirring sound in his chest, audible to him when in bed at night.

He acknowledged no history suggestive of previous cardiorespiratory disability, or of hypertension or rheumatic fever. He did recall having been told several years previously that his blood serology was positive, but he had not undertaken antiluetic treatment.

On examination his blood pressure was recorded as 165/30 mm. of Hg; pulse, 96; respiratory rate, 24 per minute. Over the precordial area a thrill was readily palpable, accompanied by a loud decrescendo musical murmur extending throughout diastole. The murmur, resembling almost exactly the sound of a dove's coo, could be heard over the carotid and subclavian arteries and down the course of the aorta to the upper lumbar area, where it was louder on the right side than on the left. In a quiet room the sound was faintly audible at a distance of two to three inches from the precordium. Moist râles were present in both lung bases posteriorly, but there was no peripheral edema or distention of the liver or neck veins. Pulsation was visible in the retinal arterioles.

An electrocardiogram on admission showed a sinus rhythm and no abnormalities other than minor T-wave changes of a nonspecific nature. The chest x-ray revealed definite cardiac enlargement, predominantly of the left ventricle. Blood serologic examinations were positive for syphilis, and antiluetic therapy was instituted.

This patient obtained a moderate degree of symptomatic relief from digitalis and diuretic treatment. Six weeks after his first visit to the clinic, however, he developed symptoms of coronary insufficiency without electrocardiographic evidence of myocardial infarction. On the more than 20 occasions he was examined his "dove-coo"

murmur was found to remain unchanged. April 24, 1954, four months after his initial visit to the Heart Clinic, he died suddenly at home. No autopsy was obtained.

Two graphic recordings of the heart murmur in this patient are shown in figure 1.

Case 2. A colored male, 52 years of age, was first seen in the emergency room of Roper Hospital June 4, 1954, complaining of severe burning pain in the lumbar area and throughout both lower extremities. The pain was of about an hour's dura-

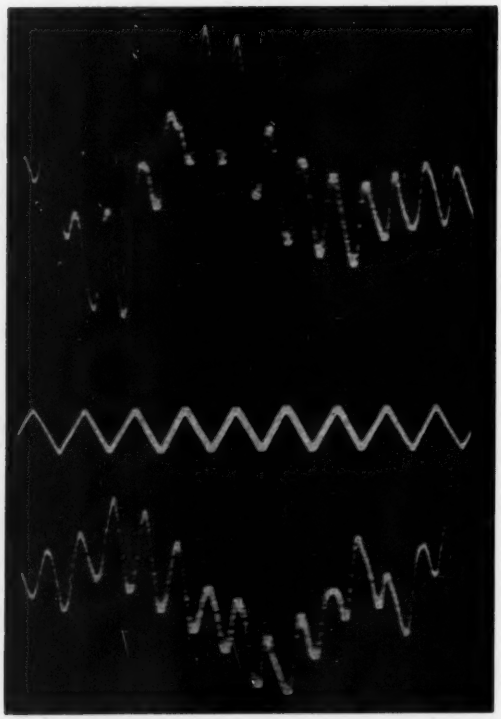

FIG. 1. *Case 1.* The tracings above and below are those of the dove-coo sound recorded from the precordium; that in the middle is a triangular wave time marker of 100 c.p.s. for reference.

The time interval between successive peaks (or nadirs) of the time trace is 0.01 sec., each entire trace thus representing less than 0.1 sec.—a fraction of the entire murmur. These tracings were recorded without effective filtering out of the low frequencies so that the sound vibration appears, as it actually is, superimposed on a wave of about 20 c.p.s. Frequency of this portion of the murmur is 158 c.p.s.

tion, and had largely subsided by the following day. No apparent cause for this acute episode was demonstrable during his subsequent five day admission to the hospital. On all his examinations a grade II to III dove-coo murmur was noted as an incidental finding, and blood pressure determinations ranged from 110 to 135 systolic and 30 to 60 mm. of Hg diastolic. Physical examination was otherwise not remarkable except for low grade fever and minimal pretibial edema.

Studied again in the Heart Clinic in September, 1954, the patient acknowledged

no symptoms referable to the cardiovascular system at any time. In particular, there was no history of lues or of antiluetic therapy, and no recollection of past trauma to the chest, rheumatic fever, or serious illness of any kind. He was not aware of the presence of any unusual sound in his chest. The dove-coo murmur was as noted on previous examination, with its area of maximal intensity along a line from the aortic area to the apex, with maximal transmission over the carotid

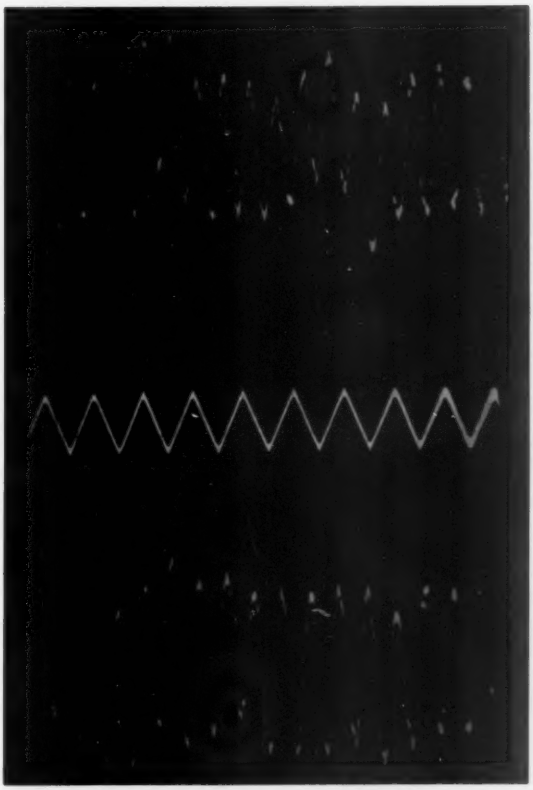

FIG. 2. *Case 2.* Sound tracings above and below, with 100 c.p.s. time marker in center. This was recorded from the third intercostal space at the left sternal border. The murmur was of much less intensity than that of case 1. Its fundamental frequency is approximately 184 c.p.s.

arteries and down the chest posteriorly to the left costovertebral angle. The sound was not audible at a distance and was not accompanied by a palpable thrill. Minimal pulsation was discernible in the retinal arterioles.

Electrocardiograms showed T-wave inversion in all standard and precordial V leads. Repeated blood serologic tests for syphilis were negative.

Chest x-rays revealed moderate left ventricular dilatation, with approximately 1 cm. further enlargement of the transverse diameter of the heart since his hospital

admission three months previously. Pulmonary emphysema with large blebs was seen in the right lung fields, and a minimal amount of pleural effusion was present at both costophrenic angles. Fluoroscopically there was a marked increase in pulsation of the ascending and transverse aorta without, however, any demonstrable aortic dilatation. This patient has been able to return to work without treatment and has remained essentially asymptomatic during his four months of observation.

Tracings of the diastolic sound in this case may be seen in figure 2.

Discussion

Both of these cases presented the same dove-coo type of diastolic murmur with clinical evidence of aortic valve insufficiency. The rapid downward course of case 1, with abrupt onset of congestive failure, the appearance of

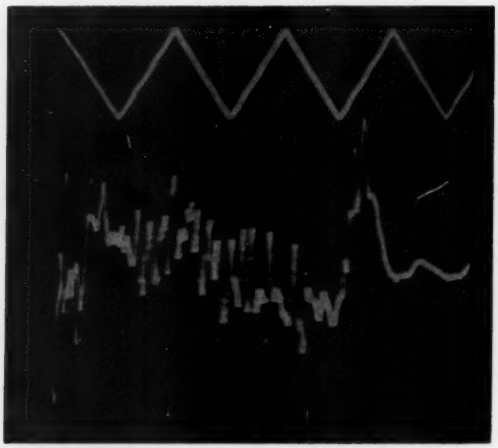

Fig. 3. Sound tracings of the systolic murmur in a child demonstrated on cardiac catheterization to have an interatrial septal defect. The recordings were made from the third left intercostal space on the precordium.

A. The entire murmur, occupying the interval between the first and second heart sounds. Its time marker above is 10 c.p.s.

angina pectoris, and sudden death presumably from impairment of the coronary circulation, is typical of most cases reported in the literature of eversion or rupture of a valve cusp in syphilic aortitis. Etiology of the valvular defect in case 2 remains uncertain. That the aortic regurgitation in this patient may be of short duration is suggested by x-ray evidence of comparatively rapid cardiac enlargement over his three month period of observation. The murmur of case 2, while of much less intensity and of slightly higher pitch than that of the first case, is identical in all other respects. Both patients manifested on every examination a prolonged musical diastolic murmur, conspicuously different from all other types of murmurs, and simulating closely the cooing of a dove.

The Sound Tracings: Recorded graphically, both dove-coo murmurs are

seen to consist of virtually pure sine wave oscillations. That is, they are composed of one continuous, regular vibration—a musical tone—much as that emitted by a single structure (e.g., a violin string) vibrating at its resonant frequency. In case 1 the frequency is 158 c.p.s. and in case 2 it is 184 c.p.s. Whatever harmonic frequencies may be present must be of a very minor amplitude, so that only the fundamental appears in the tracings. A slight decrease in frequency with time is measurable in the

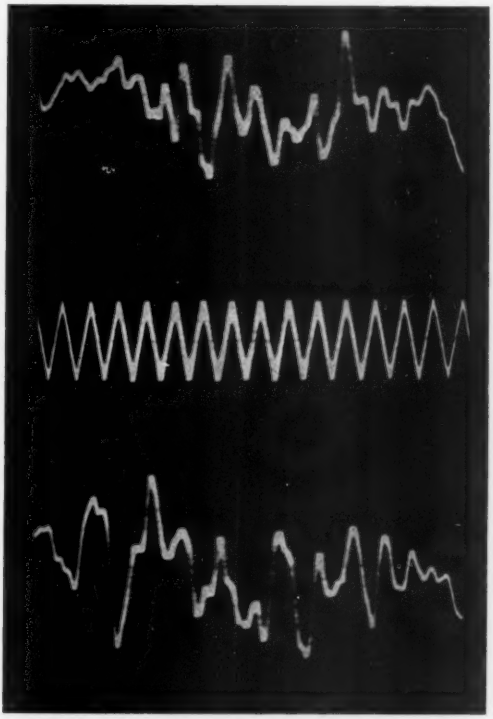

FIG. 3 B. Two recordings of portions of the same murmur but made with an expanded time scale. The triangular wave in the center is a calibrating frequency of 100 c.p.s.

recordings of both cases,* corresponding to the characteristically descending pitch of the murmur.

Ordinary murmurs, on the other hand, comprise a mixture of many frequencies. Their wave forms tend to be grossly irregular, like those of figures 3 and 4. Rather than showing a single sustained vibration, they are made up of a seemingly random assortment of rapid and slow vibrations

* This decreasing frequency is more readily apparent in recordings of the entire murmur than in those illustrated here which, as may be seen by reference to figure 3, depict only a time segment of the whole diastolic sound.

in varying proportions. This is commonly described as a *noise* type of pattern, which results from many structures vibrating simultaneously, or from the "forced" vibration of a single structure in response to continuous actuation of irregular frequencies. Occasionally brief runs of more or less

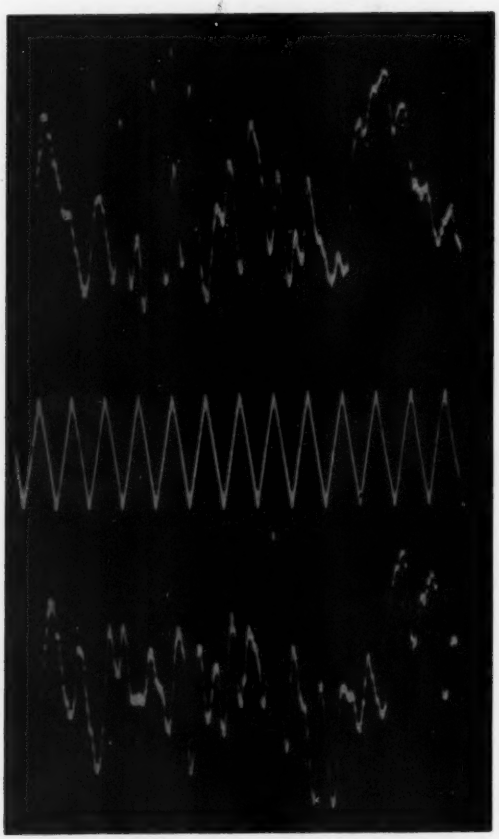

FIG. 4. Two tracings of an ordinary non-musical diastolic murmur arising from aortic regurgitation. This was recorded from the precordium of a 47 year old male with luetic aortitis and a blood pressure of 170/40 mm. of Hg.

regular oscillations appear in such murmurs, which may be noted on auscultation to possess some degree of "musical quality." An approximation * of the frequencies involved in the murmur of figure 3 would appear, by com-

* An approximation arrived at by measurement of the width of cycles or portions of cycles on tracings of non-sinusoidal wave forms is, at best, a very rough approximation and is used here mainly for illustration. Actually, some frequencies higher than those given can be demonstrated to be present by Fourier analysis of the wave forms which also takes into account the "rise time" or steepness of waves as a measure of frequency.

parison with the 100 c.p.s. time marker, to be from about 50 to at least 160 c.p.s. On the same basis the sound patterns of figure 4, those of an ordinary nonmusical diastolic murmur recorded from another case of aortic regurgitation, may be seen to include frequencies of 50 to over 200 c.p.s. It is significant that, in general, most of the higher frequency waves are of obviously smaller amplitude than those of lower frequency. Oscillations of very low (subaudible) frequency, far greater yet in amplitude, have been largely suppressed by filters in the electronic amplifier, so that all those below 30 c.p.s. appear in these tracings at less than 15% of their actual amplitude.

Genesis of the Dove-Coo Sound: On the basis of the previous pathologic studies and the nature of the sound itself, one might speculate as to the possible mechanism of production of the distinctive murmur in these cases.

That the sound arises from the vibration of a structure at its resonant frequency (natural period of vibration) is evident from the sinusoidal wave form. There seems little doubt that the vibration is initiated by the regurgitant flow of blood downward across a deformed aortic cusp. Three different types of deformity are described as being associated with this sound: that of eversion of the cusp edge, that of laceration or tearing of the cusp along its margin or line of attachment, or that of frank perforation as from rupture of a cusp aneurysm. The functional condition common to all these deformities is that the cusp, or a major portion of it, no longer supports a column of blood and is left free to vibrate in the stream. And, of course, competence of the aortic valve is abruptly decreased. Whether the frequency recorded represents the natural period of vibration of the remaining cusp or the segment of aorta to which it is attached is problematic. Several factors indicate that the latter is the case: the intensity of the sound which suggests vibration of more than a tiny leaflet; transmission of the sound prominently along the course of the aorta and its branches;* and last, the descending pitch of the tone, corresponding to decreasing tension of the aorta as its pressure falls during diastole.

One might wonder why a musical tone is not produced in all cases of aortic regurgitation where, as Hope notes, there is "presentation of an edge to a stream." It is apparent, however, that in the undeformed cusp there is rapid flow of blood on only one side of its edge, and that the cusp contains a quantity of blood capable of considerably damping its vibration. This condition does not obtain in one which is ruptured or not securely anchored and is thus left free to vibrate in the blood stream. Similarly, it is conceivable that an occasional musical quality in a murmur might arise through vibration of a pedunculated vegetation or perhaps of one of the chordae tendineae.

Audibility: As a general rule, diastolic murmurs are of less intensity

* This characteristic transmission of the diastolic dove-coo murmur upwards and out along the arterial tree is cited by Levine and Harvey [13] as evidence against the generally accepted concept that murmurs are transmitted with maximal intensity in the direction of blood flow.

than systolic murmurs. This is understandable in view of the lower pressures (and, presumably, lower velocities) involved in movement of blood during the diastolic portion of the cycle. It is then the more remarkable that the murmur most frequently audible at a distance from its site of origin should be a diastolic one. A plausible explanation for this may be derived from observation of the wave form and frequencies recorded in figures 1 and 2.

In the first place, the condition of resonance increases the amplitude of vibration. It is a well recognized fact that a structure will vibrate at a

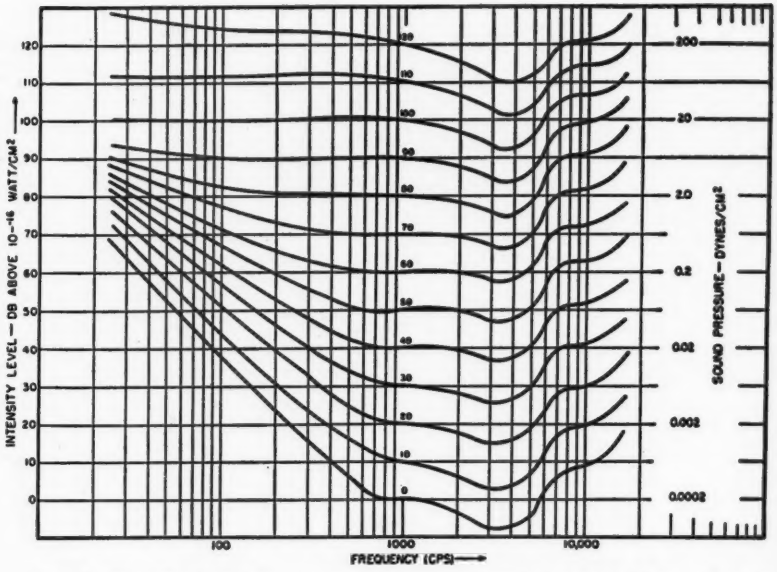

FIG. 5. The Fletcher-Munson curves of average human hearing. These show the relative intensities (in decibels) of sounds of various frequencies required to produce a sensation of equal loudness, a tone of 1,000 c.p.s. being the reference frequency. Curves for low intensity levels are much steeper, indicating a progressively decreasing responsiveness to low frequencies as the audibility threshold is approached.

much greater amplitude for a given stimulus if allowed to do so at its natural period of vibration. A regular, periodic wave form of a sinusoidal nature results. This doubtless accounts for the disproportionately high intensity of the dove-coo as compared with other diastolic murmurs.

Most cardiac sounds and murmurs are completely inaudible to the human ear unless they are conducted to the ear through an enclosed system such as that provided by the stethoscope or by placing the external auditory canal directly against the precordium. This is mainly because, without an enclosed pathway for acoustic transmission, there is insufficient coupling or transfer of vibrational energy from the chest wall to the tympanic membrane

for these relatively low intensity, low frequency vibrations to be perceived as sounds. It is possibly true that in an adequately quiet room one might be able to hear an occasional loud murmur at a short distance. But the experience is apparently so rare that it receives special mention in the literature. Certainly the intensity of heart sounds that reaches the ear under such conditions is extremely low.

Audibility, however, depends also upon a second factor: the pitch, or frequency of a sound, which governs to a great extent the ear's responsiveness to it. Particularly is this significant at *low intensity* levels, where the human ear is much less sensitive to tones of low frequency than to those in the middle audio range. At the intensity threshold of audibility the ear's inequality of responsiveness is such that a tone of 40 c.p.s. must be several hundred times the intensity (more than 25 decibels) of a tone of 150 c.p.s. to be heard at all. This characteristic of normal human hearing is illustrated in the Fletcher-Munson curves of figure 5 and is relevant to all auscultation, with or without a stethoscope. Hence intensity of the higher frequency components of a murmur is a far more significant factor in determining its degree of audibility than is the over-all intensity of the murmur. And the dove-coo, like the whirring, clicking, splashing or churning sounds —all of which may be assumed to have prominent constituents in the higher frequency range as well as high over-all intensity—would most likely be heard at a distance from the precordium.

Summary

1. Clinical observations of the "dove-coo" murmur, a specific diastolic murmur of conspicuously musical quality and associated with aortic regurgitation, are reviewed.

2. Previous pathologic studies of cases manifesting this sound have revealed eversion, laceration or rupture of one or more aortic valve cusps. The resulting abrupt increase in load on the left ventricle, and usual decrease in blood flow to the right coronary artery, have been cited as the basis for the generally poor prognosis denoted by the appearance of this murmur.

3. Tracings of the murmur in two cases, recorded with an expanded time scale on a cathode-ray oscilloscope, reveal it to be composed of a virtually pure sine wave.

4. Some considerations as to the remarkable degree of audibility and the possible genesis of this musical murmur are discussed. The ear's greater sensitiveness to sounds of relatively higher frequency, which is especially notable at low intensity levels, is a significant factor in auscultation of all sounds and murmurs.

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PREPONDERANT LEFT-TO-RIGHT FLOW THROUGH A VENTRICULAR SEPTAL DEFECT IN THE PRESENCE OF PULMONARY STENOSIS *

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Until recently there have been few reported cases of a left-to-right shunt through a ventricular septal defect in the presence of pulmonary stenosis. There are now available several papers dealing with this unusual combination.[1-8] Examples of left-to-right shunt in the presence of pulmonary stenosis have also been reported in which other anomalies also occurred, such as anomalous pulmonary venous drainage,[9, 10] atrial septal defect,[1] aortic-pulmonic communication,[11, 12] and ruptured sinus of Valsalva.[11, 13] We have had an opportunity to study three adult cases of "acyanotic Fallot's tetralogy." [5]

Methods

After premedication with barbiturates, local procaine anesthesia and procaine amide, cardiac catheterization was done. Utilizing a standard 0–75 cm. resistance wire pressure transducer, we recorded vascular pressures directly on heat-sensitive paper. Blood samples were obtained from the chambers of the right side of the heart and the pulmonary artery. Following catheterization, arterial blood was obtained by direct femoral puncture and the oxygen consumption was estimated with a closed system spirometer.

The oxygen content and capacity of the various blood samples were determined by the manometric method of Van Slyke and Niell. Using the right atrial blood as the mixed venous sample, we estimated the systemic flow by the direct Fick principle.

Case Reports

Case 1. A 20 year old man had been known to have a heart murmur since the age of one year. It was subsequently noted that he easily became short of breath on exertion and that this was associated with cyanosis of the lips. The patient led an active life, with certain restrictions imposed by the appearance of dyspnea and cyanosis on exertion. At the age of 19, after a prolonged walk, he experienced spasm of his extremities, hyperpnea and extreme cyanosis without loss of consciousness, which were relieved by oxygen inhalation for 10 minutes. An identical attack occurred one year later after exertion; it lasted two hours and subsided without the administration of oxygen. The patient claimed that the same amount of exertion previously had not hindered his physical activities. There was no history of squatting.

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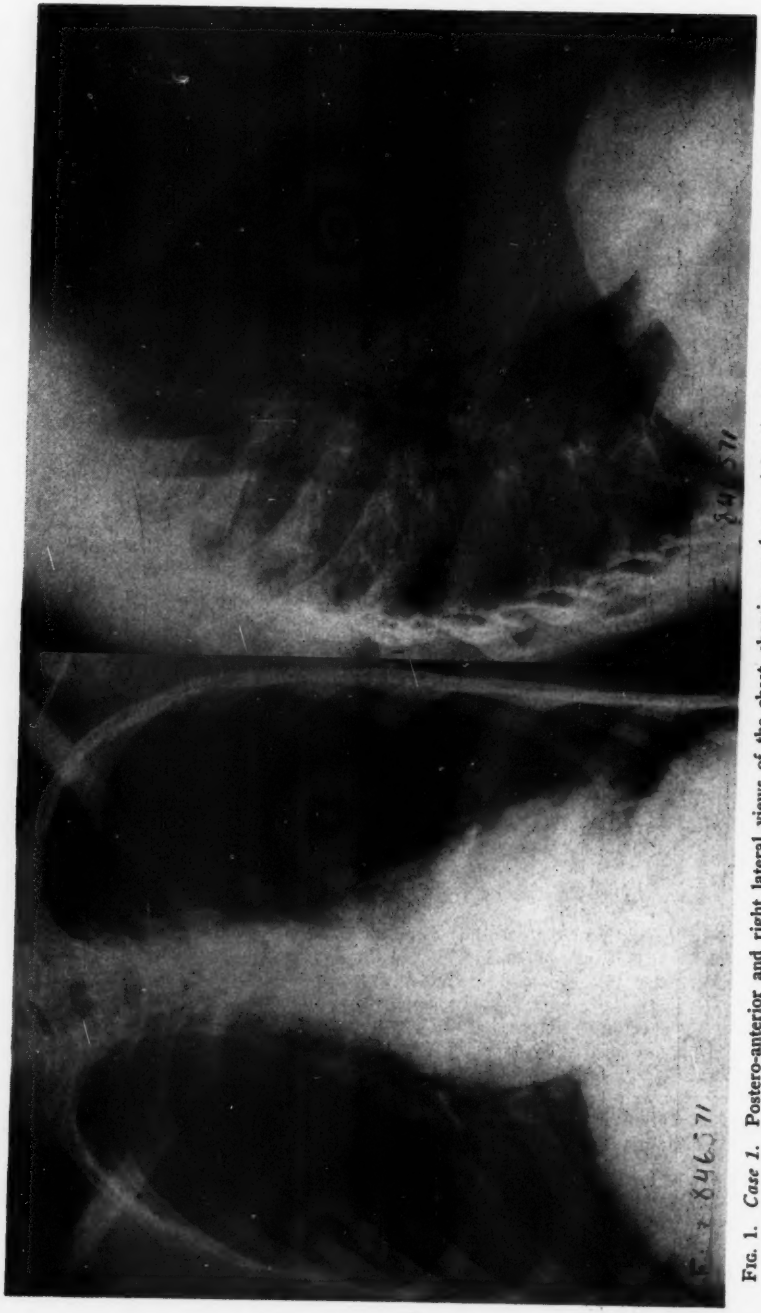

FIG. 1. *Case 1.* Postero-anterior and right lateral views of the chest, showing moderate right ventricular enlargement and a prominent left pulmonary artery segment. The lung vasculature appeared normal.

The patient had had the usual childhood diseases and, in addition, pneumonia at the age of one year.

Examination revealed a fully developed adult without apparent cyanosis at rest. There were clubbing of his fingers and a pigeon-like deformity of the chest. The pulse was regular and the blood pressure 110/68 mm. Hg. The heart size was within normal limits and no thrill was felt. A loud, harsh systolic murmur was heard in the third intercostal space just to the left of the sternum. The pulmonary second sound was barely heard, being partially obscured by the systolic murmur.

Blood examination revealed a hemoglobin of 17 gm. per 100 c.c. and an erythrocyte count of 5.7 million per cubic centimeter. Electrocardiographic findings were consistent with right ventricular preponderance (prominent R wave in aVR and V_1) and the frontal plane electrical axis was plus 120°. The PR interval was 0.20 second.

On radioscopy (figure 1), the retrosternal space was exaggerated and a generalized increase in radiability of the lung fields was noted. Moderate right ventricular enlargement was present. The pulmonary artery segment was prominent. The pulmonary vascular pattern appeared to be normal.

TABLE 1

Cardiac Catherization Data

Case	Pressure, mm. mercury			Oxygen Saturation, per cent				Estimated Pulmonary Flow (L./min.)	Estimated Systemic Flow (L./min.)	Estimated Left-to-right Shunt (L./min.)
	Pulmonary Artery (mean)	Right Ventricle	Right Atrium (mean)	Pulmonary Artery	Right Ventricle	Right Atrium	Femoral Artery			
I a	8	86/2	3	76	78	65.0	94.2	4.30	2.74	1.56
b	—	86/4	3	—	(hi) 79 (lo) 71	73	95	6.12	4.39	1.73
II	12	138/6	5	78	69	69.5	93	5.00	3.05	1.95
III	9.5	80/8	4.5	76	73	64	91	6.16	3.49	2.67

Cardiac catheterization was carried out. The results are presented in table 1 (a). On withdrawal of the catheter from the pulmonary artery to the right ventricle, the systolic pressure changed from 8 mm. of Hg to 86 mm. of Hg, indicating a considerable degree of pulmonary stenosis, since there is normally no detectable gradient between these two chambers. The blood oxygen saturation was virtually the same in the pulmonary artery and the right ventricle, but on further withdrawal of the catheter into the right atrium a distinct difference in saturations was observed, the values being 78% in the right ventricle and only 65% in the right atrium. This latter finding is consistent with an inflow of arterial blood into the right ventricle from the left ventricle through a ventricular septal defect, despite the presence of significant pulmonary stenosis and right ventricular hypertension. The sudden sharp change in the pressure curve on withdrawing the catheter from the pulmonary artery to the right ventricle suggested that the pulmonary stenosis was localized and hence valvular rather than infundibular in origin. No evidence for an infundibular chamber, or "third ventricle," could be detected.

An exercise test was done (table 2). Preëxercise and postexercise blood samples were obtained from the brachial artery through a small, indwelling polyethylene tube. The patient was exercised on a treadmill for one and one-half to two minutes at a speed of three miles per hour on the level. Before the end of the test the patient became extremely cyanotic, lost consciousness and became incontinent of urine and feces. The test was not repeated following surgery.

Following completion of the studies surgery was performed. On inspection of the heart, the pulmonary artery was normal in size but a small infundibular chamber with a definite muscular wall was noted. The pulmonary valve was stenotic. There also was marked infundibular pulmonary stenosis, the channel measuring less than 0.5 cm. in internal diameter. An attempt at dilatation was considered hazardous because of the patient's condition. A pulmonary valvulotomy was done. The immediate postoperative course was complicated by a left hemothorax.

Three months postoperatively a second cardiac catheterization was attempted. The catheter could not be passed into the pulmonary artery, but high and low ventricular blood samples were obtained. The results differed little from the preoperative study (table 1 b).

Comment: This patient had, therefore, a pulmonary stenosis of the valvular and infundibular type, with a shunt through a ventricular septal defect that was preponderantly left-to-right on rest but was converted to right-to-left on exertion. An attempt at surgical correction was unsuccessful.

Case 2. A 27 year old woman was admitted with a complaint of dyspnea on exertion. At birth the patient had been found to have a heart murmur as well as a slight bluish tinge to the lips. She did not start grade school until the age of eight

TABLE 2

Exercise Test in Case 1

Brachial Artery	Prior to Exercise	At the End of Exercise
Oxygen content	20.06 vol. %	6.53 vol. %
Oxygen saturation	92.5%	29.2%

Oxygen capacity 21.36 vol. %

because of the frequent occurrence of upper respiratory infections and pneumonia. At the age of 12 she had "arthritis" involving the joints of her lower extremities, said to be due to rheumatic fever. She had subsequent episodes of migratory arthralgia. On admission, dyspnea on exertion was her main concern, associated with occasional episodes of precordial pain that radiated to her left arm and to the back. Cyanosis had recently become more apparent than during her early life and was noted especially on exertion. She denied squatting or fainting spells on exertion.

Examination revealed a well developed woman with a plethoric face. There was a suggestion of clubbing of the fingers. Her pulse was regular. The blood pressure was 126/80 mm. Hg. The heart was not enlarged. A systolic thrill was felt over the third intercostal space to the left of the sternum, and a loud systolic murmur was best heard in this area. The pulmonic and aortic second sounds were equal.

The transverse diameter of the heart as revealed by cardiac fluoroscopy was normal. There were right ventricular enlargement and straightening of the pulmonary artery segment, with moderate prominence of the aortic arch (figure 2). The hilar and peripheral pulmonary vessels were within normal limits. The electrocardiogram was consistent with right ventricular preponderance (prominent R wave in aVR and V_1), and the PR interval was 0.20 sec. The hemoglobin was 17.7 gm. per 100 c.c., and the erythrocyte count was 5.1 million per cubic millimeter. The hematocrit was 55%.

Table 1 presents the results of cardiac catheterization. While the catheter was being withdrawn from the pulmonary artery into the right ventricle the pressure

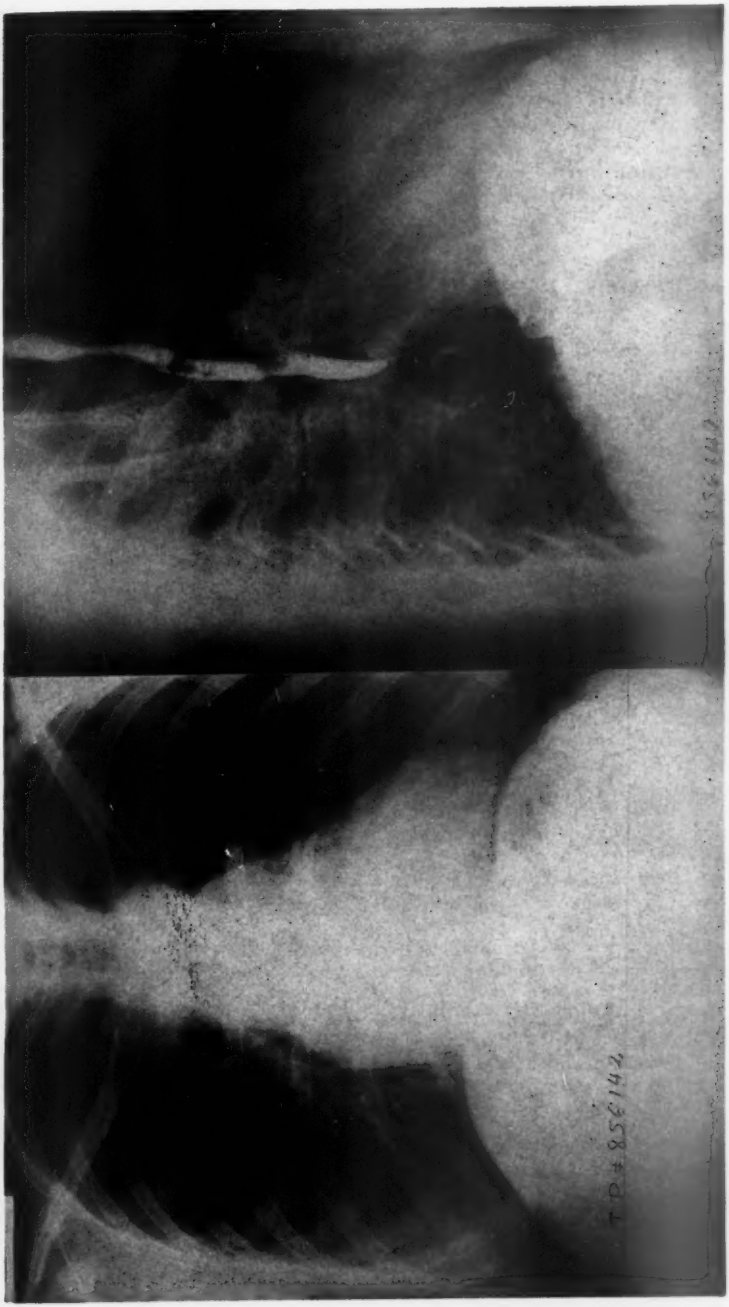

FIG. 2. *Case 2.* Postero-anterior and right lateral chest films showing normal lung markings and slight but definite right ventricular enlargement.

tracing revealed a sudden increase of the systolic pressure, suggesting pulmonary valvular stenosis. The results of the blood oxygen analyses were thought to be consistent with a high ventricular septal defect, since the ventricular sample was taken near the tricuspid valve. Frequent ventricular premature beats prevented the withdrawal of a high ventricular sample. Though the flow across this defect was thought to be preponderantly left-to-right, a small amount of right-to-left flow was suggested by the decreased oxygen saturation of the arterial blood.

At thoracotomy neither an infundibular bulge nor a poststenotic dilatation could be identified. An incision proximal to the pulmonary valve opened into an infundibular chamber with a thick muscular wall. Incision of the infundibular stenosis was carried out. Postoperatively the patient became progressively cyanotic and died five hours later.

Postmortem examination revealed bilateral atelectasis of the lungs. The bronchi, however, were free of visible obstruction. The right lung weighed 275 gm. and the left 250 gm. The right ventricular wall measured 2 cm. in thickness at the base. There was an infundibular stenosis, the inside diameter of which measured 1.5 cm. The pulmonary artery circumference was 3.5 cm. The aortic valve measured 5.5 cm. in circumference. A defect high in the interventricular septum measured 1.6 cm. in circumference. The left ventricular wall measured 1 cm. in thickness at the base. The final pathologic diagnosis was tetralogy of Fallot with unexplained bilateral pulmonary atelectasis.

Comment: This case definitely falls into the category of infundibular pulmonary stenosis, with a left-to-right shunt through a ventricular septal defect.

Case 3. A 16 year old girl had apparently been in good health up to the age of 10 years, at which time she developed an upper respiratory tract infection. Subsequently it was noticed that she became cyanotic on exertion, even though she was very active. During the three months prior to this study the patient became aware of "spells" that accompanied hard physical activities. These spells consisted of dyspnea, weakness, headaches without syncope, and cyanosis of the lips and nailbeds.

On examination she appeared well developed, without apparent cyanosis or clubbing of the fingers. The pulse was regular and the blood pressure 130/74 mm. Hg. A left parasternal precordial bulge was noted. The heart size was normal. A systolic thrill was felt over the third intercostal space to the left of the sternum, and a loud systolic murmur was best heard at this area. The pulmonic second sound was partially obscured by the murmur.

The hemoglobin was 14.0 gm. per 100 c.c. The electrocardiogram was consistent with right ventricular preponderance (prominent R wave in aVR and V_1), and the PR interval was 0.20 sec.

On radioscopy (figure 3), the heart was normal in size. Moderate right ventricular enlargement was present. The pulmonary vascular markings appeared to be normal.

Cardiac catheterization was carried out. The results are presented in table 1. Upon withdrawal of the catheter from the pulmonary artery into the right ventricle a sudden increase in the systolic pressure was noted. The catheterization findings were suggestive of pulmonary valvular stenosis associated with a ventricular septal defect and a "preponderant" left-to-right shunt through the defect.

Comment: This patient is included in this report in the absence of anatomic proof. The slight oxygen unsaturation of the femoral artery blood suggests a very slight right-to-left shunt.

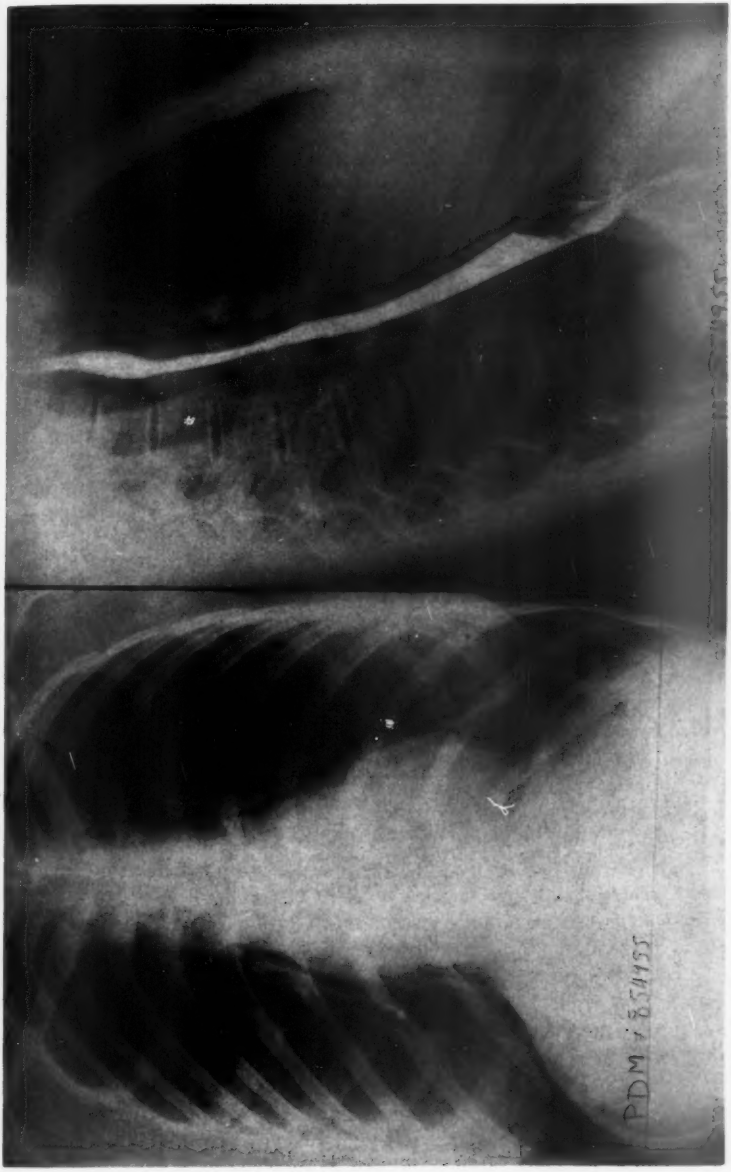

FIG. 3. *Case 3.* The heart was not increased in size in the postero-anterior view but definite right ventricular enlargement is present. The lung fields are normal.

Discussion

Three adult patients have been presented as pulmonary stenosis, associated with a ventricular septal defect and a "preponderant" left-to-right shunt, as evidenced by the analysis of the oxygen content of blood obtained from the chambers of the right side of the heart. Only a small right-to-left shunt was present, as indicated by the relatively normal oxygen saturation of the arterial blood. Physiologic studies conclusively demonstrated the primary abnormalities (pulmonary stenosis, ventricular septal defect), and defined the direction of the shunt, but failed to identify the type of pulmonary stenosis in two of these cases.

The direction of blood flow across a ventricular septal defect depends on the direction of the pressure gradient across the septum. The direction of the pressure gradient is dependent, in turn, upon the balance between the sum of all of the resistances in the greater circulation as opposed to the sum of all the resistances in the lesser circulation, plus the flow in each circuit. In the presence of an uncomplicated ventricular septal defect the lesser circulation resistances are many times smaller than those in the greater circulation. Therefore, even though pulmonary blood flow may be greater than systemic blood flow, a much higher pressure is necessary to create flow in the systemic circuit than in the pulmonary circuit. This excess in left ventricular pressure over right ventricular pressure results in a left-to-right shunt through a simple ventricular septal defect.

The effect of pulmonary stenosis is to increase the resistance in the lesser circulation resulting in a rise in right ventricular pressure at a given flow rate. This tends to decrease the pressure gradient from left to right and, if the stenosis becomes severe enough, may completely abolish the gradient or reverse it. Flow follows the same course. In the cases presented the most important factor determining the direction of flow was the severity of the pulmonary stenosis.

Upon exertion, particularly in case 1 (and cases 2 and 3 by history), the left-to-right shunt through the ventricular septal defect was converted into a right-to-left shunt. During exercise, a proportionate increase in the blood flow through the skeletal muscles occurs to keep them working efficiently.[14] This is accomplished by vasodilatation and a reduction in the peripheral resistance. This would lead to a lowered blood pressure if the heart could not maintain the required increase in its output. In the lesser circulation, the right ventricular outflow resistance is fixed and cannot decrease proportionately in order to maintain the balance previously present (i.e., at rest) across the defect because it is dependent, in these cases, on the stenotic area. Further, the resistance in the pulmonary stenotic area may increase due to the presence of turbulent flow. As a result, the direction of the pressure gradient across the ventricular septum will be reversed, and the shunt will be converted into a right-to-left one.

The slightly desaturated arterial blood at rest suggests a possible cyclic

reversal in the pressure gradient across the septal defect during each cardiac cycle. The magnitude of the gradient in normal people and in these patients may be instantaneously different during the various parts of the cardiac cycle. That the direction of the gradient also changed during the cycle is especially suggested by the saturation of the arterial blood at rest in cases 2 and 3. The pressure gradient may have been positive from right-to-left during a small part of the cycle.

The sudden fall in the arterial oxygen tension, resulting from the change in the direction of the shunt, may have caused the fainting in case 1.[15] Acute right heart failure has been postulated as the cause of syncope in such cases.[16] There is no direct evidence for this, however.

Failure to recognize the presence of infundibular pulmonary stenosis in cases 1 and 2 was due to the recording of a sudden concomitant change in both the diastolic and systolic pressures upon withdrawal of the catheter from the pulmonary artery, in spite of attempting to eliminate all technical factors[17] that might alter the pressure recording. Probably the short distance between the two stenotic areas (valve, infundibulum) was responsible for this error in diagnosis.

One point in regard to the interpretation of catheterization data in such circumstances requires emphasis. Cases have been reported in which the difference in systolic pressure between the right ventricle and pulmonary artery was as low as 15 mm. Hg.[18] Personal experience with atrial septal defects both before and after surgical closure has shown that pressure differences of this magnitude across the pulmonary valve are not diagnostic of pulmonary stenosis in the presence of a large left-to-right shunt. Such differences have been observed preoperatively and are absent after the shunt has been abolished, indicating clearly that in the face of increased flow through a normal pulmonary valve, relative or functional pulmonary stenosis may occur. Currently available data would indicate that a pressure gradient of 30 to 40 mm. Hg between right ventricle and pulmonary artery may exist in the presence of a normal pulmonary valve and a large left-to-right shunt.

The problem of surgical management of this combination of lesions is controversial. At the time these cases were studied it was thought that release of the pulmonary stenosis would be desirable, but it was also realized that such a procedure could be complicated by an increase in the left-to-right shunt through the ventricular septal defect. Such an alteration in dynamics could conceivably be more disturbing to cardiac function than the original combination. If the concept of the pulmonary stenosis being "protective" to the lung vasculature is correct, relief of the pulmonary stenosis might be followed by the development of pulmonary hypertension and eventually the syndrome of Eisenmenger's complex. These theoretic considerations have not as yet been confirmed or denied by clinical observation.

The ideal surgical approach to such cases would involve eradication of the pulmonary stenosis and closure of the ventricular septal defect. Such

an operation would be completely corrective. Operations of this type have been successfully carried out on a limited basis in children with anatomic and functional tetralogy of Fallot, using the technic of controlled cross circulation and open cardiotomy.[18] Further improvement of this technic may well make such a procedure available to this type of adult case, and at this time it would seem unwise to recommend a simple pulmonary valvulotomy for the patient with pulmonary stenosis and a left-to-right shunt through a ventricular septal defect.

Summary

1. Three examples of physiologic variant of Fallot's tetralogy are reported in which the preponderant shunt at rest was from left to right.

2. The most important factor in determining the pressure gradient, and hence the direction of flow across the defect, seems to be the severity of the pulmonary stenosis.

3. The shunt may reverse with exercise, since an increased cardiac output in the presence of a fixed right ventricular outflow tract resistance may elevate the right ventricular pressure to a level in excess of that in the left ventricle.

4. Cyclic variations in the pressure gradient across the septal defect may account for slight arterial unsaturation at rest, although the major flow is from left to right.

5. This combination of anomalies is theoretically completely correctable by surgical technics now available.

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NEOPLASTIC INVASION OF THE HEART AND PERICARDIUM *

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It is the purpose of this report to call attention to the frequency of neoplastic invasion of the heart and pericardium and to present the clinical features which may facilitate antemortem diagnosis. The observations are derived from a clinicopathologic study of 315 deaths from malignant tumors in a series of 1,007 consecutive autopsies at this hospital, and from a partial review of the medical literature.

Frequency and Nature of Cardiac Metastases

The incidence of cardiac metastases has been variously reported to be from 0.24 to 6.45% [1-3, 22] of all autopsies, as compared to an incidence of 0.0017% for primary tumors of the heart. Hence it follows that the incidence of cardiac involvement in any autopsy series will depend upon the frequency of neoplastic diseases as a whole. This probably accounts for the differences noted in table 1.

Table 1

The Incidence of Heart or Pericardial Metastasis in Unselected Autopsies

Author	Number of Autopsies	Pericardial or Heart Metastasis	Incidence %
Pollia and Gogol (1936)	12,000	29	0.24
Scott and Garvin (1939)	11,100	118	1.06
Dimmette (1950)	1,818	38	2.09
DeLoach and Haynes (1953)	2,547	137*	5.37*
Cohen et al.	1,007	65	6.45

* Included macroscopic metastases only.

It is less easy to explain the variation in incidence of cardiac metastases in autopsy reports based upon the total number of malignant tumors. According to Friedberg,[4] the heart or pericardium is involved in from 6 to 11% of fatal malignant tumors. Other authors [1-3, 5-8, 22] report an incidence of 2 to 21% (table 2). The higher incidence in some series may reflect a greater interest of the staff in advanced neoplastic disease, thus correlating with the longer duration of life and the greater opportunity for metastases to occur. Or, the higher incidence in some studies may be due to a predominance of the particular types of neoplasms in which cardiac metastases are most frequent. In some instances the differences may measure the care

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TABLE 2

The Autopsy Incidence of Heart or Pericardial Metastasis in Patients with Malignancy

Author	Total Cases	Pericardial or Heart Metastases	Metastases %
Willis (1933)	323	20	6.1
Burke (1934)	327	14	4.3
Pollia and Gogol (1936)	1450	29	2.0
Scott and Garvin (1939)	1082	118	10.9
Dimmette (1950)	455	38	8.4
Prichard (1951)	4375	146	3.3
Bisel et al. (1953)	500	105	21.0
DeLoach and Haynes (1953)	980	137*	13.9*
Cohen et al.	315	65	20.6

* Included macroscopic metastases only.

with which the autopsies are performed, the findings recorded and coded for reference.

Although cardiac metastases may arise from malignant neoplasm in almost any organ, carcinoma of the breast, bronchogenic carcinoma, malignant melanoma and the malignant lymphomas constitute the most frequent offending lesions (table 3). In Scott and Garvin's [2] series, carcinomas of the bronchus and breast together accounted for 48% of all cases.

TABLE 3

Primary Sites of Tumors Metastatic to Heart or Pericardium

Primary Site	Scott-Garvin		Prichard		Cohen et al.	
	Cases	%	Cases	%	Cases	%
1. Breast	16	13.6	23	15.8	23	35.4
2. Lung (bronchus)	41	34.7	16	11.0	12	18.5
3. Malignant lymphomas	16	13.6	18	12.3	10*	15.4
4. Malignant melanoma	5	4.2	18	12.3	5	7.7
5. Mouth or lip	1	0.8	2	1.4	3	4.6
6. Stomach	2	1.6	10	6.8	3	4.6
7. Cervix	2	1.6	7	4.1	2	3.0
8. Kidney	3	2.5	8	5.5	1	1.5
9. Pancreas	4	3.2	1	0.7	1	1.5
10. Esophagus	4	3.2	—	—	—	—
11. Parotid	—	—	—	—	1	1.5
12. Liver	3	2.5	—	—	—	—
13. Thymus	—	—	—	—	1	1.5
14. Prostate	2	1.6	—	—	—	—
15. Ovary	1	0.8	3	2.0	1	1.5
16. Vulva	—	—	—	—	1	1.5
17. Colon or rectum	1	0.8	4	2.8	1	1.5
18. Tongue	—	—	6	4.0	—	—
19. Penis	—	—	4	2.8	—	—
20. Testis	—	—	2	1.4	—	—
21. Miscellaneous (1 or 2 cases per organ)	17	14.4	24	16.4	—	—
Total Malignant Neoplasms	118	99.1	146	99.3	65	99.7

* Myelogenous leukemia, 3; lymphatic leukemia, 3; Hodgkin's, 2; lymphosarcoma, 1; giant follicular lymphoblastoma, 1.

Metastases were found in the heart in about one third of all tumors of these two organs.

Most of these tumors reach the heart or pericardium by direct extension from neighboring intrathoracic organs. The second most frequent pathway is by invasion of the pulmonary veins and implantation within the myocardium via coronary artery embolization. Less commonly, hematogenous dissemination from more distant sites and retrograde lymphatic extension may occur.[5]

The cardiac involvement may consist of (1) neoplastic lymphangitis, (2) miliary infarction due to tumor emboli in the coronary vessels without gross metastases, (3) single or multiple nodules, presumably due to hematogenous dissemination, or (4) diffuse infiltration. In some instances of the latter the tumor may encroach upon and fill the cardiac chambers or thicken the myocardial or pericardial walls,[5] or even obliterate the pericardial cavity.[9, 10]

Pericardial metastases are more common than myocardial metastases, and endocardial metastases are rare. Since endocardial involvement is believed to occur by surface implantation, Prichard[7] assigns the rarity of valvular implants to the relative avascularity of the endocardium; and Coller and associates[11] believe that preëxistent valvular damage is a requisite for tumor implantation. These latter authors reported the first case in which the mitral valve was involved. The involvement in the six cases previously reported had been tricuspid in five and aortic in one.

Diagnosis of Cardiac Metastasis

Neoplastic invasion of the heart or pericardium may be relatively asymptomatic, and diagnosis usually is extremely difficult. Of some 500 autopsy-proved cases reported in 1951,[7] an antemortem diagnosis of metastases to the heart had been made in only 21.[3] In many of the cases with cardiac metastases there has been no disturbance of cardiac function, and death has been a result either of the primary lesion or of metastatic involvement of other organs. Sudden death has also been observed[9] in the absence of prior evidence of heart disease.

Scott and Garvin[2] noted that cardiac insufficiency occurred in seven of their 118 cases of cardiac metastases with no instances of cardiac decompensation in a control group of 100 malignant tumors not involving the heart or pericardium. They concluded that cardiac failure developing without apparent cause in a patient with a known malignant tumor is the most important finding indicative of cardiac metastasis, while abnormalities of cardiac rhythm or evidences of pericardial disease are only suggestive signs.

Since the electrocardiographic changes depend primarily on the location and extent of tumor tissue, no electrocardiographic patterns diagnostic of cardiac tumor can be expected. Scott and Garvin[2] and Siegel and Young[12] found premature auricular contractions, auricular flutter and auricular fibrillation to be the predominant arrhythmias; in all but one of their cases with arrhythmia, autopsy disclosed involvement of the atrium.

In accordance with the anatomic schema proposed by Ravid and Sachs,[18] certain syndromes may suggest involvement of the pericardium, great veins or myocardium. Infiltration of the pericardium or the right atrium may be indicated by signs of cardiac tamponade, by a rigid, nonpulsating cardiac border on fluoroscopy, or by electrocardiographic evidence of pericarditis. A persistent or rapidly reforming pericardial effusion, especially if serosanguineous or frankly hemorrhagic,[14, 15] constitutes strong presumptive evidence of neoplastic involvement of the pericardium. The demonstration of tumor cells in the pericardial fluid, by either the Papanicolaou technic or by section of the sediment, is diagnostic.[14, 16, 17] In this connection one should remember that a dry pericardial tap does not exclude the diagnosis, for complete adhesion of the parietal and visceral pericardium may be present as a result either of disease or of previous roentgen therapy.[18]

Unexplained heart failure, often of sudden onset and intractable nature, is the most common clinical manifestation of myocardial metastasis,[2, 4, 10, 19] although cardiac decompensation may also occur as a result of pericardial or endocardial involvement. Unexplained sinus tachycardia, premature auricular or ventricular contractions, auricular flutter or fibrillation, bundle branch block or complete heart block[2, 14, 19] with Stokes-Adams syndrome probably constitute the second most frequent type of manifestation of myocardial involvement. These disturbances of rhythm or conduction are usually encountered in cases with metastatic invasion of the atria, particularly the right atrium.[4] If a coronary artery is encircled or encroached upon, angina may be present.[4] Finally, myocardial involvement may be manifest by irregularity of the cardiac contour on x-ray or by localized or generalized enlargement of the cardiac silhouette which, on serial films, may be seen to be progressive in nature.[4]

In addition to the clinical picture and routine roentgenologic studies, the angiocardiogram has become an aid in the diagnosis of cardiac neoplasm since it was first suggested for this purpose by Mahaim[15] in 1945. Coulter[20] has warned, however, that although gross lesions involving the right atrium should be readily demonstrable by this method, the left atrium is ordinarily not well visualized and filling defects might not be recognizable.

It should also be mentioned that Lübschitz and associates[21] in 1949 successfully employed artificial pneumopericardiography to outline the heart prior to confirming the diagnosis of a primary heart tumor by recovery and identification of neoplastic cells from pericardial fluid.

Report of Our Series

In the series of 1,007 consecutive autopsies performed in this hospital during a 57 month period ending December, 1952, 315 malignant neoplasms are recorded. In 65 of these the heart, pericardium or both were involved, an incidence of 6.5% of all autopsies, or 20.6% of all the malignant neoplasms coming to autopsy. Although this is approximately twice the in-

cidence reported by Friedberg,[4] it agrees with the recent work of Bisel and associates,[8] who found 106 cases (21.2%) of cardiac metastases in 500 consecutive autopsies in patients dying with neoplastic diseases at The Memorial Center for Cancer and Allied Diseases, New York City. DeLoach and Haynes,[22] including only macroscopic tumors, reported an incidence of 13.9% of metastases in an autopsy study of 980 cases of malignant disease.

In our series, the patients' ages at the time of death ranged from 20 to 84 years, the majority occurring in the fifth, sixth and seventh decades of life (table 4). The series is weighted by the absence of a pediatric service in this hospital.

The pericardium was involved in 39 cases, four of which were microscopic lesions only; of the 42 instances in which myocardial involvement was found, 17 were microscopic only; and seven cases with endocardial involvement were noted, of which one was microscopic only. Thus there was no significant difference between the incidence of pericardial and of myocardial metastases, except that a greater proportion of the latter were only microscopic lesions.

TABLE 4

Age Distribution of Patients with Metastasis to the Heart or Pericardium, The George Washington University Hospital

Age	No. Cases
1–19	0
20–29	2
30–39	7
40–49	13
50–59	21
60–69	12
70–79	9
80+	1
Total	65

In keeping with the experience of others, our series included very few endocardial lesions. Valvular implantation was found in two of these, in each of which the mitral valve was affected; in the second case the aortic valve was also involved. In the first patient there was adenocarcinoma of the stomach and in the second, adenocarcinoma of the floor of the mouth.

Fourteen primary sites were represented in this group of 65 cases (table 3). Twenty-three (35.4%) originated in the breast, 12 (18.5%) in the bronchus, 10 (15.4%) were included among the malignant lymphomas, and five (7.7%) were malignant melanomas. Together these comprised 50 cases, or 76.9% of the primary sites. The other primary sites in our series included the stomach (three cases); mouth (three cases); cervix uteri (two cases); and the kidney, pancreas, ovary, colon, parotid, thymus and vulva (one case each).

Among the 65 patients in our series there were 25 with congestive heart failure, 15 with arrhythmias, and 14 with pericardial effusion, either ante

mortem or at necropsy. In the 14 subjects with pericardial effusion the fluid was clear in seven and serosanguineous in three; in the remaining four frank hemopericardium was present. Pericardial or cardiac involvement was diagnosed correctly in three of nine patients ir whom signs of cardiac compression were detected. In addition, an antemortem diagnosis of cardiac metastases was suspected in two other patients, one on the basis of an irregular cardiac silhouette in the roentgenogram, and the other on the basis of a transient pericardial friction rub.

The following are the subjects in whom an antemortem diagnosis of cardiac metastases was made or suggested:

Case Reports

Case 1. This patient was a 45 year old white male with bronchogenic carcinoma. The clinical picture included cardiac failure with cardiomegaly, premature ventricular contractions, and signs of cardiac compression. Neoplastic invasion of the heart was diagnosed on the basis of the clinical picture. Autopsy disclosed involvement of the pericardium and the superior vena cava.

Case 2. This patient was a 66 year old white male with bronchogenic carcinoma. The diagnosis of cardiac invasion was suggested on the basis of an "irregular, shaggy appearance" of the cardiac silhouette in the chest film. At necropsy there was hemopericardium, and tumor was evident in the epicardium in the region of the great vessels.

Case 3. This patient was a 55 year old white male with malignant melanoma, primary in the skin of the right wrist. The diagnosis of cardiac metastasis was made in light of the findings of cardiac compression, serosanguineous pericardial effusion, auricular fibrillation and detection of cancer cells in the pericardial fluid. At autopsy the left auricular appendage was also found to be involved.

Case 4. This 39 year old colored female had adenocarcinoma of the breast. The diagnosis was made on the basis of cardiac failure, hemopericardium, and the recovery of tumor cells from the pericardial fluid. At autopsy there was hemopericardium and extensive tumor infiltration of the epicardium.

Case 5. This patient was a 64 year old white male with lymphatic leukemia. On the eighteenth hospital day a pericardial friction rub was heard and interpreted as evidence of pericardial infiltration. Although the pericardium appeared grossly normal at autopsy, microscopic invasion of the myocardium was present.

In some instances, cardiac symptoms due to metastatic lesions of the heart may be the presenting complaints in a patient without apparent evidence of neoplastic disease or of heart disease. This is particularly true when a malignant tumor has been excised some years previously and there is no evidence of local or regional recurrence. Unexplained pericardial effusion or unusual mediastinal or cardiac shadows on the roentgenogram in such instances should arouse a suspicion of cardiac metastasis.

When evidence of neoplastic heart involvement is discovered, a search should be made for a primary site and suitable measures instituted. Although the prognosis of metastatic tumor of the heart is grave today, this may not be true in years to come, when more effective methods of therapy become available. The detection of neoplastic invasion of the heart or pericardium will then be of more than academic interest. Even today, many of

these patients can be helped, temporarily at least, by repeated pericardicenteses, operative drainage of the pericardium into the pleural space, judicious irradiation, or appropriate tumor chemotherapy.

Summary and Conclusions

1. The literature on metastatic tumors of the heart and pericardium has been partially reviewed and the pertinent clinical features have been described.

2. In an analysis of 1,007 consecutive autopsies performed during a 57 month period at this hospital, 65 tumors metastatic to the heart or pericardium, or both, were found among 315 malignant tumors of all kinds, an incidence of 20.6%. Diagnosis was made prior to death in three patients and suggested in two others.

3. Tumors of the breast, bronchus, the lymphoma group and malignant melanoma accounted for about three fourths of the cases with cardiac metastasis, which is in agreement with the experience of others.

4. The development of one or all of the triad of cardiac failure, cardiac arrhythmias or cardiac compression in patients known to have malignant disease should suggest the possibility of metastases to the heart or pericardium.

5. It would appear from this and other recent studies in the literature that neoplastic invasion of the heart is more frequent than was formerly believed, and should be given consideration in the differential diagnosis of heart disease.

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HEMOPTYSIS, BRONCHIAL EROSION AND BRONCHITIS *

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Hemoptysis, alarming to the patient and ominous in the eyes of the physician, often justifies the dread with which it is regarded. However, this is not invariably so, and many cases of even severe respiratory tract hemorrhage may prove benign in origin. Approximately one fourth [1] of all patients with hemoptysis will present no etiologic explanation for this symptom, even after exhaustive diagnostic studies have been carried out. Frequently such patients quickly recover their usual state of health and have no further difficulty. Obviously, then, the great majority of these individuals do not have cancer or tuberculosis or even bronchiectasis, and their hemoptysis must be attributed to a much less serious disorder. It is the authors' opinion that respiratory tract bleeding in many of these cases is related to minor inflammatory disease of the bronchial mucosa which leads to erosion or cracking of this structure, with resulting hemorrhage of variable degree, in much the same manner that inflammatory disease of the nasal mucosa may lead to epistaxis. The purpose of this paper is a presentation of the concept of hemoptysis resulting from erosive lesions of the bronchi, and a consideration of its characteristics and pathogenesis, with particular reference to relatively minor inflammatory disease, i.e., bronchitis, as a cause.

Bronchial Erosion

Pathogenesis: The bronchoscopist can give ample testimony to the ease with which the normal bronchial membrane can be made to bleed from the slightest injury. This friability renders that structure extremely vulnerable to erosion or ulceration by various disease processes. In view of the vascularity of the bronchial tree, it is not surprising that such lesions should be frequently associated with bleeding.

Expressed in simplest terms, bronchial erosion may be said to be a result of coughing and cyclic bronchial action on an area of lowered tissue resistance produced by a variety of pathologic states. Conditions responsible for the increased tissue susceptibility may be divided into two groups: (1) those arising in or adjacent to the bronchi, and (2) systemic factors (table 1). The direct impact of the majority of group 1 disorders on the bronchial mucosa requires little elaboration. However, the important rôle of rela-

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tively mild and transient inflammation as a predisposing factor in the production of bronchial erosion seems, with a few exceptions,[1, 2] to have been largely overlooked. The somewhat tardy recognition of this relationship of inflammation to bronchial bleeding appears the more puzzling since the probable mechanism involved is simple, logical and basically evolved from the changes always to be found in association with inflammatory processes. In short, the turgor produced by inflammatory edema or swelling of the mucosal structures eliminates the minute mucosal folds which normally provide for increases in bronchial caliber. Thus there occur a relative inelasticity, a reduced resistance to stretching, a predisposition to cracking

TABLE 1

Important Factors in the Pathogenesis of Bronchial Bleeding

I. Predisposing causes
  A. Bronchial
    1. Local
      a. Broncholithiasis
      b. Bronchial adenoma
      c. Carcinoma, primary and metastatic
      d. Aneurysm
      e. Telangiectasis
    2. Diffuse
      a. *Bronchitis* and bronchopneumonia
      b. Tuberculous bronchitis
      c. Bronchiectasis
  B. Systemic
    1. Hypertension
    2. Mitral stenosis (bronchial varices)
    3. Purpura
    4. Menses
II. Precipitating causes
  A. Cough
  B. Respiratory bronchial motion
  C. Direct trauma
    1. Bronchoscopy
    2. Foreign bodies

or erosion, and an exaggeration of the friability of a normally fragile membrane.

Bronchial bleeding occurring with group 2, or systemic disorders, is an expression of a general vascular defect associated with these diseases, and the bronchial tree is just one of many areas in which this weakness may show itself. For example, hypertension and purpura may be a cause for bleeding in practically any organ of the body. Although vicarious menstruation is commonly considered in the differential diagnosis of epistaxis, it is probably usually overlooked as a cause for hemoptysis. In this connection, it should be mentioned that compared with other mucous membranes, such as those of the mouth or nose, the bronchi exhibit an excessive fragility.

Through the action of these various disorders, then, an already delicate structure is further conditioned or predisposed to the stretching, traumatizing and denuding effect of such dynamic factors as a vigorous cough and the continuous changes in length and caliber of the bronchi that occur with each respiratory effort. The frequency with which a severe paroxysm of coughing precedes the onset of hemoptysis leaves little doubt as to the significance of its rôle in precipitating bronchial bleeding. The relative importance of the predisposing conditions listed in table 1 as producing hemorrhage is extremely variable. For example, a large area of bronchial ulceration caused by carcinoma or a broncholith may produce only minor blood-streaking or no bleeding at all, while it is not unusual to see a patient bleed profusely from an erosion associated with what seems to be negligible underlying pathology.

Character of the Bleeding: Although hemoptysis of bronchial origin may be associated with a variety of clinical disorders, it tends to be similar in all cases due to the common basic bronchial defect. As a result of rapid clearing of the bulk of the blood by the cough reflex, a recently expectorated specimen is likely to be bright in hue and to contain a minimum of clots.

The liquid nature of the bleeding resulting from bronchial erosion may sometimes be distinguished from that occurring with such conditions as pulmonary infarction, lung abscess, pulmonary tuberculosis and suppurative bronchiectasis. In these latter instances, bleeding occurs into infarcted lung or cavitary dead space, so that, due to stasis, blood is more likely to form dark clots prior to being coughed up.

While such a differentiation of hemoptysis on a clinical basis is not always possible, the concept has proved useful at times. Certainly, important adjunctive information may be missed by omission of a simple inspection of a fresh sputum specimen.

Any attempt to discuss all of the many causes of bronchial erosion and hemoptysis would lead us too far afield. For the purposes of our discussion we have chosen bronchitis for further consideration; it illustrates the problem well and has not, in our experience, been fully appreciated as a cause for significant respiratory tract bleeding.

Bronchitis and Hemoptysis

In describing the pathology of bronchitis most standard texts state that variable degrees of mucosal desquamation, denudation or atrophy occur.[3-5] It would therefore seem that hemoptysis should be a not infrequent association, although the majority of clinical works [4, 5] tend to minimize its occurrence. It is our impression, however, that hemoptysis is not uncommonly associated with this disorder. In addition to our own experience, this contention is further supported by the work of Opie, Blake, Small and Rivers,[6] who conducted a detailed study of the clinical features of influenza during the 1918 pandemic. They observed that ". . . hemorrhage from the mucous

membranes was common. Epistaxis occurred in 12 per cent of the cases and was often profuse. The sputum contained fresh blood in varying amounts in 24 per cent of the cases; 51 per cent of the cases developed signs of bronchitis." Pathologic studies of 250 autopsies disclosed that, "In those who have died with pneumonia following influenza the large bronchi (with cartilage) are intensely injected, so that the mucosa has a deep red color. . . . Superficial injury to the bronchi is not infrequently evident in the larger bronchial branches; superficial loss of epithelium is indicated by erosion of the surface. . . . Occasionally . . . there is necrosis of epithelium. . . . Complete loss of epithelium occurs, usually in small patches. . . . The blood vessels of the mucosa are engorged. There is sometimes edema or hemorrhage. . . . With the bronchitis of influenza the small bronchi (with no cartilage or mucous glands) show every stage of transition from early acute inflammation characterized by accumulation of polynuclear leucocytes within the lumen, engorgement of blood vessels, and infiltration of the wall with polynuclear leucocytes, through various stages of destructive changes to complete disappearance of the bronchial wall. . . . In the early stages of acute bronchitis, hemorrhage is frequently associated with the lesion. . . ."

Clinical Picture: The experience of coughing up blood is so alarming to an individual that he is not apt to volunteer other complaints. It is important that the doctor whose aid he seeks not allow himself to become similarly alarmed, for a thoughtful, unhurried interview has a soothing effect and will yield less dramatic but vital information. A history of an antecedent upper respiratory infection, perhaps described as a "chest cold," "grippe" or "the flu," when associated with cough, is important in indicating an underlying bronchitis. This may be of variable severity and duration, but if of recent onset is more likely to be of etiologic significance. Fever and other systemic signs of inflammation, though not always present, are helpful in incriminating an infectious process. Sputum containing pus is of similar importance.

The bleeding itself is likely to begin with coughing or as a salty taste in the mouth, which is followed by spitting up fresh blood. Bleeding may be profuse but usually does not last for more than a few days. There is then more or less complete recovery, with no harmful effect on the patient's health.

The Roentgenogram: In the majority of cases the chest roentgenogram is within normal limits, except possibly for some exaggeration of the vascular markings. Occasionally this increase in markings will warrant a diagnosis of bronchopneumonia, but for the purposes of this discussion there is no difference in the bronchial changes of bronchitis and bronchopneumonia. The chief function of the roentgen-ray lies in its value in ruling out frank pulmonary causes of hemorrhage. The hilar structures should be closely examined for the presence of a calcific nucleus which might be eroding a bronchus. Unilateral hilar thickening immediately suggests carcinoma.

Bronchoscopy: A negative or almost negative chest film, coupled with a consistent clinical picture, may constitute strong evidence that the bleeding has been caused by an underlying bronchitis; nevertheless, bronchoscopy is essential. While the chances of visualizing the active bleeding sources are best if the examination is performed while the patient is still expectorating blood, a certain amount of discretion is indicated. Little is to be gained if flooding of the bronchi and bronchoscope with blood necessitates almost constant aspiration by the unfortunate endoscopist.

The usual bronchoscopic findings are a more or less diffuse injection of the bronchial mucosa, which traumatizes even more readily than the normal structure and may contain one or more shallow ulcers. Variable amounts of blood are encountered. In some instances there is little gross injection around the erosion, but a biopsy generally reveals the presence of inflammation (figure 1). A biopsy is usually indicated, and appropriate material should be forwarded to the laboratory for cytologic examination and study for tubercle bacilli, fungi and pyogenic organisms.

Differential Diagnosis: Whenever hemoptysis is encountered a variety of disorders should immediately suggest themselves to the physician. Tuberculosis, bronchogenic carcinoma, bronchiectasis, lung abscess and pulmonary infarction are all important causes of respiratory tract hemorrhage which can usually be quickly eliminated. From a clinical standpoint, the absence of pleuritic chest pain is of value in ruling out pulmonary infarction. The fresh, liquid nature of the blood is likewise against the presence of this condition. Although bronchogenic carcinoma, lung abscess and pulmonary tuberculosis are frequently suggested by the clinical picture, these bits of information cannot be relied upon, and it is imperative that a chest x-ray be obtained to rule out conclusively the presence of these diseases. A long history of cough and recurrent bouts of respiratory infection and hemoptysis suggests bronchiectasis rather than a simple bronchitis, and indicates a need for a bronchogram at a subsequent date.

During the routine physical examination a bleeding point in the mouth and throat can be excluded. If the patient is a female in her fertile years the possibility of vicarious menstruation must be considered, and it need hardly be added that a blood pressure determination and the exclusion of some defect in the clotting mechanism are essential. Likewise, the murmur of mitral stenosis must be sought in all instances. The presence of calcified peribronchial or paratracheal lymph nodes warrants consideration of broncholithiasis, and requires careful questioning of the patient with reference to the expectoration of gritty material.[7] Body section roentgenograms are useful in determining the exact relationship of the calcific focus to the bronchial tree. The need for bronchoscopy has already been stressed, and its value in detecting the presence of a bronchial adenoma is of course well recognized.

Treatment: Once it has been determined that an individual is bleeding from nothing more serious than bronchitis with erosion, the problem of

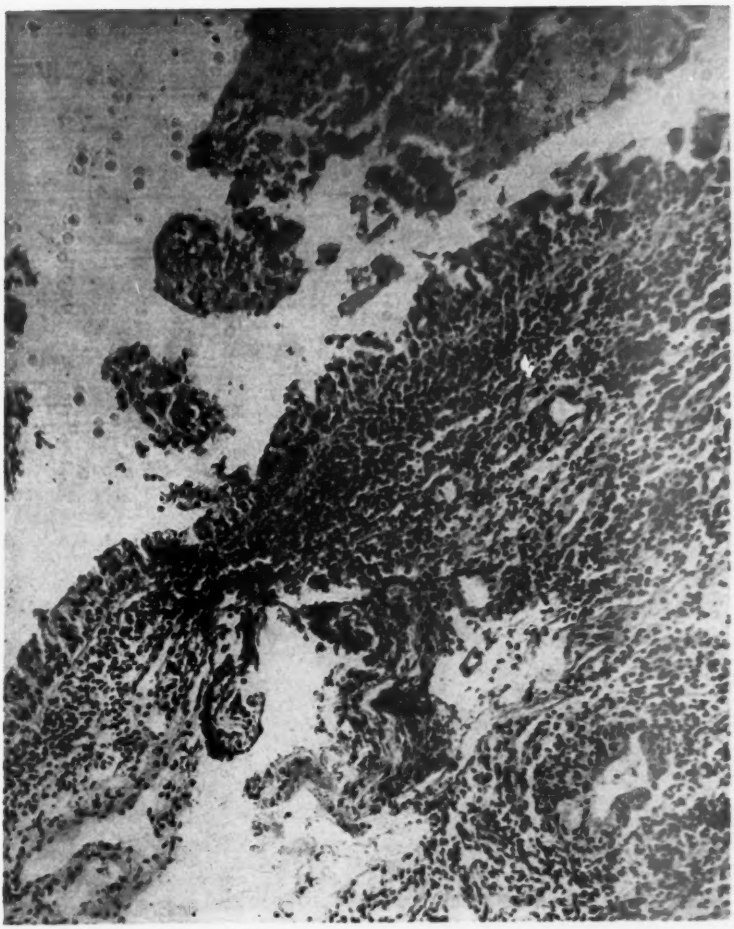

FIG. 1. *Case 1.* Mucosal biopsy near site of ulceration, showing intact epithelium with intense submucosal inflammatory reaction.

therapy is relatively simple. This consists primarily of rest in bed, gentle suppression of the cough reflex, and antibiotics. Cultures with sensitivity studies may give an indication of the antibiotic best employed; however, the process is usually under control by the time this information is available. Furthermore, as is the case with bronchopneumonia,[8] sputum cultures frequently yield bacteria normally found in the human nasopharynx. Penicillin is generally effective. Local applications to simple erosions of the bronchus have been recommended by Vinson,[2] but our patients have done well without the benefit of these measures.

Case Reports

Case 1. A 36 year old white male boilermaker was admitted to the Veterans Administration Hospital, New Orleans, Louisiana, on January 18, 1953, for management of hemoptysis. Several weeks before admission he developed grippal symptoms, feverishness, chills, aching discomfort over the left side of the chest, and a persistent cough productive of about one-half cup of yellow sputum daily. Despite bed-rest and symptomatic therapy by his private physician, the symptoms became more severe. On the day before entry the patient suddenly coughed up an estimated pint of bright red blood and therefore sought hospitalization. Physical examination disclosed a temperature of 101° F., blood pressure of 135/88 mm. of Hg, and pulse rate of 108, but was not otherwise remarkable. A chest roentgenogram taken at the time of admission revealed only minimal exaggeration of the left hilar markings. A complete blood count was normal. The patient was placed on complete bed-rest, and penicillin (300,000 U every eight hours) was begun. He continued to bring up small amounts of blood. On the third day of hospitalization bronchoscopy was performed. The trachea appeared normal down to the carina; however, the left main bronchus, the left lower lobe bronchus, and the orifice of the left upper lobe bronchus were moderately edematous and markedly hyperemic. There were occasional small bleeding points scattered throughout the length of the left main bronchus, and within the lower lobe bronchus, near the openings of the segmental bronchi, there were two small bleeding ulcers larger than those previously seen. A biopsy taken at this point was subsequently reported as showing chronic inflammation (figure 1) and superficial ulceration of the bronchial mucosa (figure 2). The right main bronchus and the visible portions of its branches appeared normal. Shortly after his admission a sputum culture was positive for *Staphylococcus aureus* and *Neisseria catarrhalis.* Repeat blood count, platelet count, bleeding time, clotting time, clot retraction, examination of four sputum concentrates for acid-fast bacilli, several blood cultures and an electrocardiogram were normal. The patient became asymptomatic by the fifth hospital day and was discharged on January 26.

Case 2. A 33 year old colored male laborer was admitted to the Veterans Administration Hospital, New Orleans, Louisiana, on August 20, 1952. One week before admission he developed a "cold," characterized by malaise, fever, sore throat, and a cough productive of moderate amounts of blood, averaging about a teaspoonful with each effort. He stated he had done this repeatedly until he was finally hospitalized. There was a past history of repeated respiratory infections occurring about every four or five months since a bout of pneumonia in 1945. Each episode resembled the one prompting the present hospitalization, being characterized by fever, sore throat, productive cough, and the presence of varying amounts of blood in the sputum. These illnesses would last two to five weeks, and were separated by more or less asymptomatic intervals. On physical examination the temperature was 99.6° F.; pulse, 70; blood pressure, 110/65 mm. of Hg. The patient appeared healthy, and the heart, lungs and remainder of the examination were normal. A blood count was normal. Chest roentgenogram showed only minimal accentuation of the hilar markings. On bronchoscopy there was noted a small ulceration in the right main stem bronchus about 2 cm. below the carina; it bled easily to the touch. The mucous membrane of the trachea and the remainder of the bronchial tree appeared normal. (A biopsy from the region of the ulceration was later reported as chronic inflammation.) Sputum culture was positive for *Staph. aureus* and alpha streptococcus. Bronchogram and examination of several sputum concentrates for acid-fast bacilli were normal. On penicillin and bed-rest the patient became completely asymptomatic.

Case 3. A 40 year old white female drug addict was admitted to the Veterans Administration Hospital, New Orleans, Louisiana, on January 23, 1953, with hemoptysis. On the day before entry she had developed a cough, chills, fever, dyspnea,

FIG. 2. *Case 1.* Mucosal biopsy at site of ulceration, showing gradual transition of epithelium from columnar to cuboidal type, with complete disappearance of epithelial cells at margin of actual ulceration (arrow).

a poorly defined pain over the left posterior chest, and generalized aching. The cough became productive of bright red blood. There was a past history of recurrent attacks of asthma since 1945. On physical examination the temperature was 104° F.; pulse rate, 124; blood pressure, 120/74 mm. of Hg. The patient appeared acutely ill. The pharynx was mildly injected. There were generalized coarse râles, and a pleural friction rub was noted over the right anterolateral thorax. The remainder of the examination was essentially normal. Chest roentgenogram revealed prominence of the vascular markings in the base of the left lung but no other abnormalities. Complete blood count was normal. Bronchoscopy disclosed diffuse hyperemia of the

entire tracheobronchial tree. The carina was edematous, and in this region there was a small ulceration, 2 by 2 mm. in diameter, with evidence of recent bleeding. A biopsy from the region of the carina was reported as showing chronic inflammation and superficial ulceration of the bronchial mucosa (figure 3). On a program consisting of penicillin, bed-rest and analgesics, the patient rapidly became afebrile and asymptomatic from a respiratory standpoint. A sputum culture taken on admission was later reported to show *Staph. aureus* and much alpha streptococcus. Several sputum examinations for acid-fast bacilli and fungi, and a blood culture, were negative. Radiographic studies of the chest two weeks after admission failed to reveal any abnormalities.

FIG. 3. *Case 3.* Mucosal biopsy, showing area of ulceration. Arrow marks point at which epithelium ends and fibrin-filled bed of eroded area begins.

Case 4. A 38 year old white male was first found to have pulmonary tuberculosis in June, 1949, while in the Army. He was hospitalized and treated with streptomycin and para-aminosalicylic acid, and a pneumoperitoneum was induced. On these measures the patient became asymptomatic from a respiratory standpoint. The sputum became negative for tubercle bacilli in December, 1949, and there was marked regression of the pulmonary shadows. On December 1, 1950, the patient was transferred from the Army institution to the Tuberculosis Service of the Veterans Administration Hospital, New Orleans, Louisiana. Physically he appeared well, except for the presence of pneumoperitoneum. The temperature was 98.6° F., and the blood pressure 105/70 mm. of Hg. Chest roentgenogram disclosed a moderate pneumoperitoneum. An area of infiltration which appeared predominantly fibrotic in character was present in the peripheral portions of the first, second and third right anterior interspaces. The remainder of the lung fields exhibited no evidence of active disease. Examination of a large number of sputum concentrates failed to reveal any acid-fast bacilli, and on December 3 the patient was granted a leave of absence. His discharge was contemplated pending return of negative cultural reports. While on bed-rest at home he suddenly developed brisk hemoptysis amounting to about one fourth cup of blood. He returned to the hospital immediately, and the hemoptysis gradually subsided. A chest roentgenogram taken on his return showed no change in the extent or character of the pulmonary shadows. Five sputum concentrates and cultures taken during the period of active hemoptysis were negative for acid-fast bacilli. On January 3, 1951, bronchoscopy revealed a mild, diffuse redness of the entire bronchial mucosa, and on the posterior wall of the right main stem bronchus there was a small ulcer one third centimeter in diameter. Other than bed-rest, no therapy was rendered. On repeat bronchoscopy on February 5 the ulceration could no longer be visualized. Altogether, 18 sputum concentrates and cultures, and cultures of five gastric washings for tubercle bacilli, were negative during the patient's stay at the Veterans Hospital. His subsequent course remained essentially uneventful and he was discharged on February 12, 1951.

Case 5. A 21 year old colored male student was admitted to the Veterans Administration Hospital, New Orleans, Louisiana, on April 24, 1953, for investigation of a chronic cough and hemoptysis. He had been well until nine months before entry, at which time he developed a "cold" characterized by rhinorrhea, nasal obstruction, ocular exudate and productive cough. Despite the use of home remedies the cough persisted. Several days prior to admission, following a particularly vigorous fit of coughing, he brought up moderate amounts of blood and therefore sought hospitalization. On physical examination the patient did not appear ill. The temperature was 98.3° F.; pulse, 80; blood pressure, 135/70 mm. of Hg. No physical abnormalities were noted, and multiple chest roentgenograms and a blood count were normal. On bronchoscopy there was marked injection of the entire endobronchial mucosa. At the most superior portion of the carina there were several small ulcerations which bled readily when touched with the bronchoscope. On a program of bed-rest, penicillin and Gantrisin the patient rapidly became asymptomatic. Studies of the sputum, bronchial washings and gastric contents for tubercle bacilli were negative, and he was discharged on May 15.

Discussion

Most of these patients had fairly characteristic symptoms of a relatively benign condition, viz., bronchitis, and without the appearance of hemoptysis would not have been major problems. With the appearance of hemoptysis, however, the situation became complicated. Even with the accumulation

of negative evidence it was surprising to see how much attention was given by the attending physicians to the possibility of tuberculosis, and the reluctance with which the correct diagnosis was finally accepted in each instance. Such an attitude seems to be fairly widespread; and, rather than stemming from the clinically sound practice of giving priority to potentially dangerous conditions, it seems to result from an unfamiliarity with the fact that minor inflammatory changes can produce significant hemoptysis.

The history of recurrent difficulty for a number of years in case 2 is suggestive of bronchiectasis. The bronchogram, however, failed to reveal that disorder. The bronchoscopic and biopsy findings were characteristic of the condition under consideration. Others [9, 10] have also noted an occasional tendency to repeated episodes of this type of bronchial bleeding, and a similar susceptibility to recurrent benign bleeding is common from other mucous membranes, e.g., the nose.

In view of the recent history of tuberculosis in case 4, its inclusion in this study may be questioned. However, we feel that the failure of intensive efforts to demonstrate tuberculous activity during and subsequent to hemoptysis, and the rapid healing of the bronchial ulceration, effectively eliminate that possibility. It is also worthy of note that this case, although unusual, graphically demonstrates the pitfalls of complete preoccupation with the more serious causes of hemoptysis. It is conceivable that this patient might have been needlessly subjected to further prolongation of an already lengthy program of therapy if repeated bronchoscopy had not been carried out, and the occurrence of hemoptysis had been accepted without question as an absolute sign of continued tuberculous activity.

Idiopathic Hemoptysis: Although the source of bleeding was detected in each of the cases presented above, it is obvious that, due to technical limitations of bronchoscopy, the specific area of erosion cannot be visualized in all instances, and that such a set of circumstances must account for many examples of essential or idiopathic hemoptysis. This mechanism was suspected some time ago by Wessler,[9] but he considered the nature of the primary process which caused the erosion to be obscure. In each of our cases there was clinical and biopsy evidence of significant underlying inflammation, and the direct relationship of the inflammatory process to the observed areas of ulceration can hardly be denied. Vinson [2] noted similar associations in a large series of simple bronchial erosions; and in another large group of patients with hemoptysis, Jackson and Diamond [1] detected evidences of tracheobronchitis in 16.9%. While these latter workers noted ulcerations in only a few of their cases, such lesions certainly must have been present somewhere in the bronchi of the others for bleeding to have resulted. In short, then, while other possibilities, such as small areas of bronchiectasis and pulmonary infarction, as suggested by Douglas and Carr,[10] cannot be denied, there is good reason to believe that many—and perhaps most—examples of so-called idiopathic hemoptysis may be attributed to relatively

minor inflammatory disease and erosion of small bronchi beyond the bronchoscopic field. The following case will serve to emphasize this viewpoint:

Case 6. A 43 year old white female housewife was admitted to a private hospital on February 27, 1954. She had been well until two weeks before admission, at which time she developed a "deep chest cold." Initially there was a sore throat, and this was followed by a persistent cough productive of small amounts of mucopurulent material. Except for the cough, however, the patient felt well, there being no associated fever, sweats or chest pain. On the night prior to entry she strangled on a piece of food. This precipitated a severe paroxysm of coughing, during which she brought up a mouthful of bright red blood. The bleeding then decreased to small amounts of clotted material; however, the following afternoon she again coughed up about a cupful of fresh blood and was hospitalized. There was no prior history of hypertension or cardiorespiratory symptoms, and a surgical menopause had occurred many years prior to admission. On physical examination the temperature was 100° F., but the blood pressure, pulse and remainder of the examination were normal, as were a roentgenogram of the chest and a complete blood count. Bronchoscopy performed on the second day of hospitalization disclosed minimal edema and erythema of the left lower lobe bronchus, but no ulcers or other abnormalities of the tracheobronchial tree. The patient was placed on a program of strict bed-rest, penicillin, mild sedation and codeine, as needed, for persistent cough. There were expectoration of minimal amounts of mucopurulent material and a few clots during the first few days. Thereafter the patient became afebrile and completely asymptomatic, and was discharged on March 4. At the time of this writing she has had no recurrence of symptoms.

The similarity of this case to those presented previously is immediately apparent. The antecedent symptoms of cough and expectoration, the character of the bleeding, the injection of the left lower lobe bronchus, and the rapid and complete recovery on penicillin are all consistent with a presumptive diagnosis of erosion secondary to bronchitis. The sequence of events immediately preceding hemoptysis clearly demonstrates the importance of dynamic factors in the development of such lesions. Had this patient not strangled and coughed forcefully, it is conceivable that she might never have bled.

Summary

1. Although hemoptysis is often associated with serious pulmonary disease and must be regarded with suspicion by the physician, this symptom does not always imply a grave prognosis.

2. Respiratory tract hemorrhage of benign origin is more common than is generally supposed, and in many cases is the result of simple bronchial erosion produced by bronchitis.

3. The mechanism and clinical features of this association are presented, together with five illustrative cases.

4. It is probable that many and perhaps most cases of so-called idiopathic hemoptysis are to be explained on the basis of minor inflammatory lesions of the bronchi which produce erosion of the mucosa in areas not accessible to the bronchoscope.

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ENDOCRINE DISTURBANCES AND THEIR DIETETIC BACKGROUND IN UNDERNOURISHED IN MEXICO *

By Salvador Zubirán,† F.A.C.P., Francisco Gómez-Mont,‡ F.A.C.P., and José Laguna,§ *Mexico, D. F.*

In the Hospital de Enfermedades de la Nutrición in Mexico we have observed a large number of patients with chronic malnutrition. Clinical manifestations are generalized, although occasionally there is a more striking involvement of a particular organ or system.[1] As we have reported previously, there are alterations in the endocrine function which manifest themselves by a clinical picture similar to that seen in panhypopituitarism.[2, 3, 4, 5, 6, 7, 8, 9, 10] Our findings are similar to other experimental or clinical descriptions.[11, 12, 13, 14, 15, 16, 17, 18, 19, 20] According to our concept, this picture results primarily from a lowered utilization of hormones by malnourished tissues. This, in combination with other factors, leads to a concentration of hormones in the blood sufficient to inhibit the pituitary gland. The result is decreased production of pituitary hormones.

This hypothesis is based on the results of histologic, clinical, endocrine and dietetic studies of 543 patients with long-standing malnutrition. The age and sex distribution of these patients is shown in table 1; it can be seen that the great majority of patients fall between the ages of 20 and 60.

Histopathologic studies reported by us[1, 2, 3, 6, 7, 8, 9, 10] showed atrophy and involutionary changes in the anterior pituitary, adrenals, testes, ovaries and thyroid glands. These findings have been supported by others.[14, 16, 18, 20]

Clinically, the syndrome in our patients was characterized by a decreased activity of the entire endocrine system. [1, 3, 4, 5, 6, 7, 8, 9, 10]Hypogonadism manifested itself in females by breast atrophy and by amenorrhea in 50% of the young women. The males were impotent, had decreased libido and showed testicular atrophy. The loss of axillary hair, increased pigmentation of the skin and mucous membranes, and the hypotension and asthenia which occurred in all cases could be attributed to adrenal cortical hypoactivity. We found no symptoms which could be attributed specifically to hypothyroidism.

The existence of panhypopituitarism in malnutrition is also supported by hormone determinations and by endocrine function tests which we have carried out.[1, 3, 4, 5, 6, 7, 8, 9, 10] Determinations of urinary estrogens and studies of vaginal smears in 29 young women and 71 postmenopause under-

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TABLE 1

Patients with Chronic Malnutrition: Age and Sex Distribution

Age Years	Males 260	Females 283
5–14	4	2
15–19	9	11
20–39	53	85
40–59	164	138
Over 60	30	47

nourished patients revealed low estrogen activity. This hypoestrogenism occurred even in the presence of advanced hepatic lesions and frank cirrhosis.[9, 10]

The average excretion of 17-ketosteroids, which was 3.5 mg. in males and 2.4 mg. in females, indicates adrenal hypofunction and a 75% reduction in testicular function.[4, 6, 9]

A low level of adrenal activity was also suggested by positive water tests, hypoglycemia and flat glucose tolerance curves in more than half of the patients tested.[6, 7, 9]

Although some basal metabolic rates were low, we could not demonstrate hypothyroidism, inasmuch as the few determinations made on protein-bound iodine and radioactive iodine uptake were within normal limits.

We found a lowered excretion of pituitary gonadotrophins and adrenal

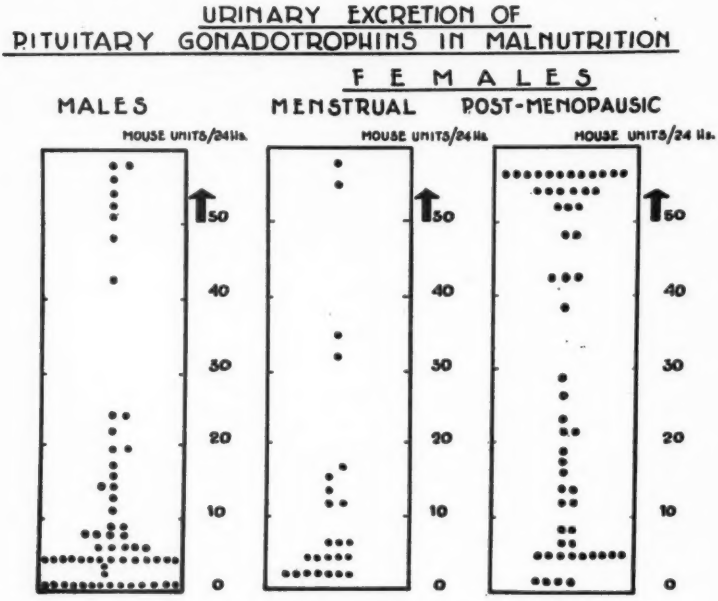

FIG. 1. Every spot represents a case studied.

response to ACTH administration, although this was poor. This has led us to support the hypothesis that glandular atrophy and decreased function of the gonads and adrenals are brought about by decreased pituitary stimulus.

This assertion is supported by the results of the excretion of pituitary gonadotrophins studied in 145 patients shortly after admission to the hospital. There is markedly diminished excretion in men and young women, as shown in figure 1. By contrast, however, the levels in 50% of the female patients in the menopause are very high, due to a lack of gonadal activity. High excretion levels were also found in two of the younger

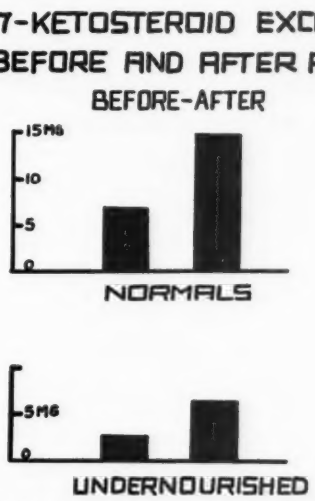

FIG. 2. The solid bars mean the 17-ketosteroid excretion in 24 hours. Twenty units of ACTH were administered intravenously during 8 hours two consecutive days. The first bar is the day before the test. The second bar corresponds to the excretion during the last day of the test.

women. In each of these cases gonadal function was absent due to active tuberculosis of the ovaries. They therefore had an excretion pattern identical to that of the patients in the menopause.

Some of the men also showed a high excretion. We were able to carry out histopathologic studies on one of these cases and found extensive fibrosis of the testes.

In the other 50% of the postmenopausal patients, malnutrition was extreme. Here, low levels of gonadotrophin excretion were found, presumably due to impaired function of the pituitary per se.

Daily application of ACTH in 12 cases produced an increase in 17-ketosteroids and a fall in eosinophils. However, this response did not reach normal levels, as can be seen in figure 2.

The functional status of the pituitary-adrenal axis was studied by measuring the metabolic response to surgical intervention in nine patients with advanced malnutrition.[21] In three of these, surgery was the only stimulus, and the response obtained was compared with that of three patients who received cortisone and three others who received ACTH. The results are shown graphically in figure 3. In no case was there loss of nitrogen. Electrolyte excretion was normal. However, there was no rebound phenomenon. The 17-ketosteroid excretion increased only when ACTH was administered and, even so, never reached normal levels. These observations indicate the existence of decreased pituitary stimulus, adrenal hypo-

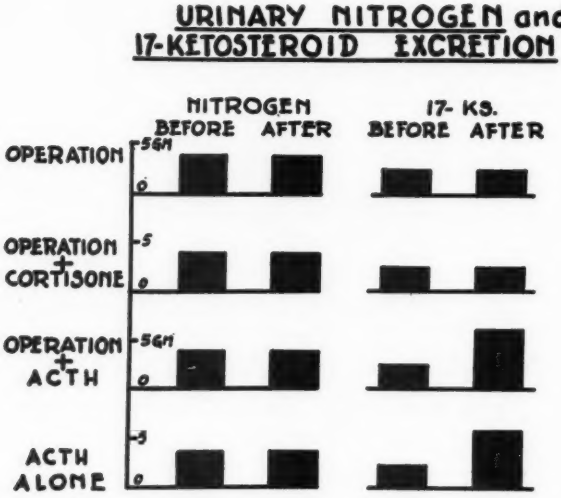

FIG. 3.

activity, and the inability of poorly nourished tissues to respond normally to applied stimuli.

By way of further study, our patients were observed over a period of months after they had been placed on an adequate dietary régime. Outstanding endocrine changes occurred during the recovery phase. Figure 4 shows the results of weekly assays of pituitary gonadotrophins over a period of several weeks in 58 patients. These show that in the initial stages of clinical improvement there is a tremendously increased excretion of pituitary gonadotrophins, which in the younger women is followed by the reëstablishment of estrogen activity and normal menstrual cycles.

In males the increase of pituitary gonadotrophins was followed by an increase in the urinary estrogen excretion, which reached an abnormally high level. This was accompanied by gynecomastia.[4, 6, 7, 9, 10] This hyper-

estrogenism, which is late to appear and transitory, is the result of pituitary stimulation and has no relation whatsoever to the status of liver function.

Subsequent serial biopsies show a gradual return of normal testicular structure.

The 17-ketosteroid levels rise slowly and reach normal levels only after a prolonged period of time.[4, 6, 7]

From these observations one can conclude, first, that the changes in endocrine function are promptly reversible; second, that hyperestrogenism

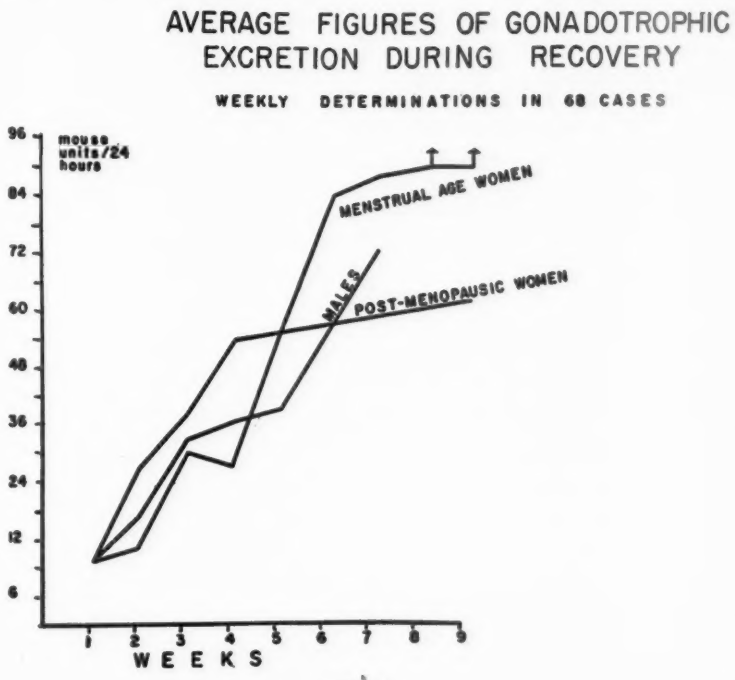

FIG. 4.

exists in malnutrition as a transitory phenomenon and in the recovery phase only; and third, that these data constitute additional support for the hypothesis that the basic cause of the endocrine changes in malnutrition is hypoactivity of the pituitary.

To determine the relation of food intake to endocrine hypofunction, we studied the diets of our patients.[6, 22, 23] We then compared these with data from dietary surveys of the general population having a similar social and economic background.[23, 24, 25, 26] These data are shown in figure 5. In the first column one can see that our patients had a caloric intake about 50% of

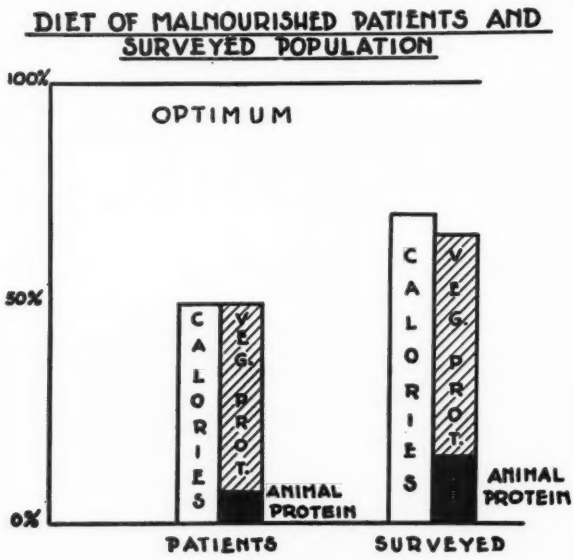

FIG. 5.

that recommended by the National Research Council.[27] This included 30 gm. of protein, of which 15% was of animal origin. The next column shows the average diet of the surveyed population. The caloric intake amounts to 70% of the recommended figure, with a protein consumption of 40 gm. a day, of which 25% is of animal origin.

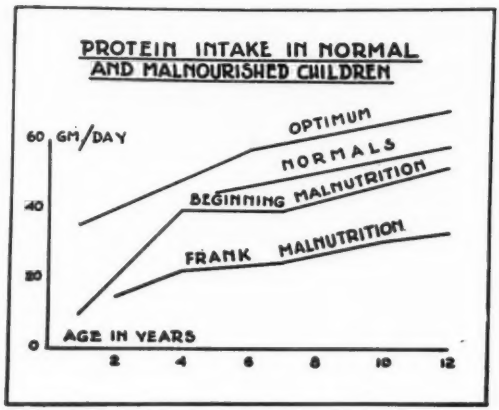

FIG. 6.

Figure 6 shows the data on apparently healthy children.[23] Protein intake is proportional to the total food consumption. Here the intake is less than 70% of the ideal and, when reduced slightly more, leads to the appearance of signs and symptoms of malnutrition to the point where hospitalization is required.

From these facts one can see that the average diet of the surveyed population is borderline for maintaining satisfactory nutrition. Either increased metabolic requirements or reduction in intake by as little as 10% or 15% upsets the balance, and signs of malnutrition appear.

Although this average diet is deficient in all respects, the most important factor is a lack of animal protein. This has been shown by us in animal experiments[29, 30] and by our studies in a group of 10 apparently healthy subjects from the rural zone.[24] When these subjects were maintained on a basic diet of corn, beans and other vegetables, without animal protein, nitrogen balance was reached, but in three subjects in whom a long-term observation was made the serum albumin was about 1 gm. lower than the initial levels. No change was brought about by adding vitamin B complex or increased quantities of corn and beans to the diet. The serum albumin reached the previous normal levels only when 20% of the vegetable protein was substituted by animal protein. Thus, basic equilibrium can be achieved by the use of vegetable protein only, but in this event the distribution of proteins in the body, as well as their turnover and mobilization, apparently becomes altered in such a way as to decrease the serum albumin. These facts show that a poor diet, deficient in all respects but mainly in animal protein, was the cause of the endocrine derangement in our patients.

We now have to consider a concept which can explain these endocrine changes. The panhypopituitarism which we found in our patients must be due either to a decreased capacity of the pituitary to synthesize hormones or to a defect in hormone liberation.

In many of our postmenopausal patients we found evidence of normal pituitary capacity as manifested by high levels of gonadotrophin excretion.

It has also been shown experimentally that malnourished animals have normal or even increased amounts of hormones in the pituitary gland,[19, 31, 32, 33, 34, 35, 36, 37, 38, 39] and that they can synthesize and liberate these hormones under stress conditions.[37, 38, 39]

We are led to the conclusion that, in such cases, the capacity of the pituitary to synthesize hormones is almost normal. Paradoxically, we have demonstrated pituitary hypoactivity and reduced excretion of gonadotrophin in men and young women with persisting though lessened gonadal activity. These facts can be explained only by an inhibitory effect on the pituitary by secretions from these target glands.

We obtained considerable support for this hypothesis from studies of a malnourished male with severe atrophy and fibrosis of the testes, and of two young malnourished females with ovarian lesions in whom high excre-

tion levels of gonadotrophin were found. Because of the total lack of gonadal activity in these cases, the inhibitory effect on the pituitary was not present.

In extreme malnutrition, however, the situation is different, for the pituitary has lost its capacity to produce hormones. This was apparent in postmenopause patients with severe malnutrition who had pituitary atrophy and a low excretion of gonadotrophins.

If we accept that there is an inhibitory action on the pituitary in patients with less severe malnutrition, how can this inhibitory action be explained when we know that the target glands show atrophic changes and reduced activity?

A possible explanation is as follows:

In malnutrition, metabolic processes are slowed[40] and thus the rates of utilization and inactivation of hormones are proportionately diminished.[41, 42] The secretions of the target glands, although greatly reduced, are not utilized or destroyed at the normal rate. Hence the blood concentration of these hormones is maintained at a level sufficient to inhibit the pituitary.

On the other hand, if the blood concentration of hormones is high enough to produce this effect, why do these patients present a picture of generalized endocrine deficiency?

In answer to this question, we propose the hypothesis that, in malnutrition, the altered metabolic processes render the tissues incapable of responding to the action of hormones in the normal manner. This concept is supported by experimental evidence from our own patients, in whom we were able to demonstrate a poor response to ACTH and cortisone administration as well as to surgery. Similarly, others have shown in experiments with undernourished rats that the response of the mammary glands to estrogens is subnormal.[43]

Thus, if the tissues cannot respond normally to the action of hormones in the blood, the end result is identical to that produced by a generalized endocrine deficiency, that is to say, panhypopituitarism.

Figure 7 is a schematic presentation of our concept of endocrine cycles in malnutrition. In the first diagram, representing the normal sequence of events, the secretions of the target glands are utilized and inactivated by the tissues. Thus the blood concentration falls below levels which can inhibit the pituitary. As a consequence, the pituitary secretes adequate amounts of trophic hormones which, in turn, stimulate the activity of the target glands.

The second diagram depicts our concept of what happens in chronic malnutrition. Here the metabolic processes are slowed; and the rates of utilization and inactivation of hormones deriving from the target glands are proportionately diminished. This decreased utilization results in a relatively high blood concentration of these hormones, leading to inhibition

of the pituitary. Thus the amount of trophic hormones is reduced, and the target glands do not receive their normal stimuli. The final result is a picture of panhypopituitarism due to the reduced amount of hormones secreted by the target glands and to the incapacity of the tissues to respond to these hormones.

The next diagram shows that, except in extreme malnutrition, the pituitary is capable of producing hormones. This capacity becomes ap-

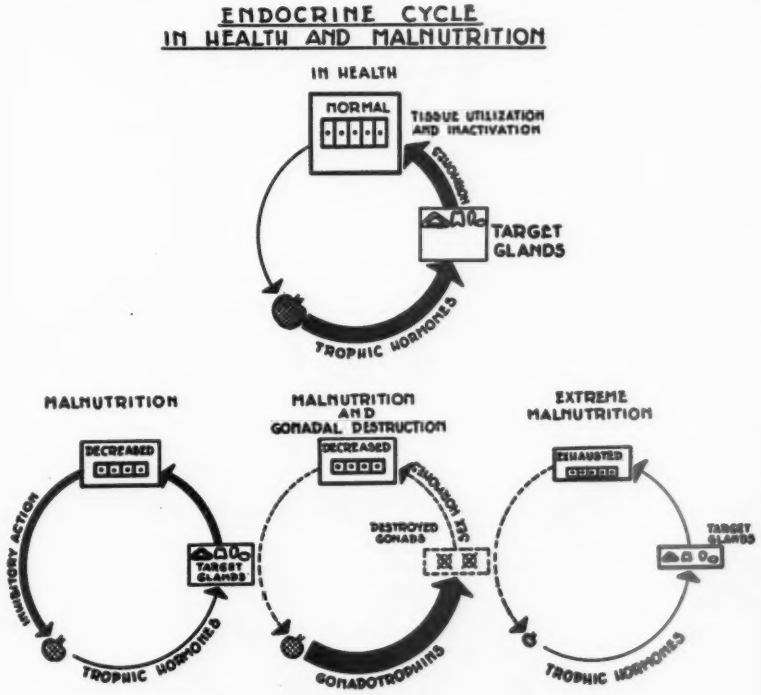

FIG. 7.

parent when in the absence of gonadal activity and the consequent lack of the inhibitory effect the gonadotrophins are secreted in normal amounts. This situation was encountered in our malnourished patients in the menopause, as well as in those with tuberculosis of the ovaries and atrophy of the testes.

The last diagram indicates the situation in extreme malnutrition. Here the tissues and all the glands, including the pituitary, are exhausted. There is a marked decrease in all types of activity, and vital functions are barely maintained.

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PITFALLS IN THE CARE OF CARDIACS*†

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To err is human. What physician has had a perfect score in practice? Only he who is not aware of the mistakes he has made. It would be well if we could learn from our own or others' experiences—and especially from the errors that we all make—in order to avoid repetitions of these costly blunders. The pitfalls in the care of cardiacs are numerous, some vital and others of little importance. The purpose of this discussion is to review some errors that I have been responsible for or that I see going on in the general practice of cardiology. Some are errors of omission, others of commission; some easily avoided, others more difficult to anticipate; some irretrievable, others lend themselves to later correction; some a matter of life or death, others of minor importance.

With each new therapeutic discovery the challenge to the medical profession increases. Oversights in the care of incurable conditions merely hurt the pride of the conscientious physician, but just as soon as methods of cure or amelioration become known the responsibility becomes great—in fact, overwhelming. It mattered little when subacute bacterial endocarditis was overlooked before the introduction of antibiotics, or coarctation of the aorta before operative relief was available. But now such errors may mean the difference between a long, useful life and early death. It is evident that even in the field of heart disease, where only two decades ago progress seemed at a standstill and the outlook far from promising, a new and painstaking analysis is necessary to protect the interest of our patients.

When a physician is confronted with a possible problem of heart disease there are several questions that he should ask himself before embarking on a program of treatment. The first is whether the patient has or has not organic heart disease. The second is, if heart disease exists is there heart failure? The third is whether there is anything peculiar about this particular problem that requires special or specific therapy, i.e., where ordinary treatment with digitalis, diuretics, etc. will be inadequate and ineffective. Only after these three questions are satisfactorily resolved can the physician embark on the customary course of therapy employed in the care of cardiacs.

It is evident that diagnosis is all-important. When the correct diagnosis has been made, patients suffering from various forms of heart failure appear to be treated quite intelligently by the average practitioner in this country at the present time. This was not true a few decades ago. At that earlier period it was a common experience for a consultant to see a critically sick

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patient and restore him promptly to good health. Digitalis and diuretics were not being properly employed. Massive hydrothorax was overlooked. Many errors in diagnosis were being made. There was a large gap between the knowledge of the expert and that of the family physician. The situation has entirely changed. The function of the consultant nowadays often consists in supporting the hand of the attending physician and comforting the family with the knowledge that everything helpful is being done. Only infrequently—and then for the most part when the diagnosis is wrong—does the consultant aid materially in the care of cardiacs. On these occasions lives may be saved or greatly prolonged.

In analyzing the first question—i.e., whether organic heart disease is present at all—a frequent error is the quick assumption that breathlessness is due to heart failure. Functional dyspnea should be easily recognizable, especially when of the "sighing" type, because such patients show nothing abnormal on physical examination and often display characteristic deep sighs. They complain of being unable to get enough air when they have overventilated and have actually inhaled three or four times as much air as they need. Furthermore, they feel short of breath without cause at rest. When an organic cardiac is breathless at rest he is obviously very sick and is likely to show ample evidence of organic heart disease, whereas the functional cases appear quite well. Another misinterpretation of the complaint of breathlessness is in confusing cardiac with bronchial or pulmonary dyspnea. Many patients with emphysema or pulmonary fibrosis are given digitalis and other cardiac therapy on the basis that they have heart failure. The character of the breath sounds, the prolonged expiration with squeaking disseminated râles, the emphysematous appearance of the chest on inspection and on x-ray examination, and the normal size of the heart and other clinical features are generally adequate to identify the true nature of the disability. Discontinuing digitalis, administering medications like ephedrine and other measures directed at the pulmonary problem often prove to be rewarding.

Another type of error involves the interpretation of various forms of pain or discomfort in the chest. The question often arises whether a patient has no heart disease whatever, or has angina pectoris. It is well known that angina may be present where nothing abnormal is detectable on the most careful physical examination, and that the diagnosis depends in most cases on the interpretation of the peculiar symptoms. When atypical, these may be difficult to appraise. Effort tests and attempts to reproduce the pain or discomfort and to obtain diagnostic changes in the electrocardiograms may then be very helpful. Even with these aids cases may yet remain obscure, because occasionally angina or coronary sclerosis may be present with negative tests, and cases without angina may show positive tests. There is one additional observation, not currently appreciated, that I have found invaluable, i.e., the carotid sinus test. When a patient is observed while he actually has chest pain and the carotid sinus is massaged for a few seconds and the heart slows considerably, if the pain is anginal in character it will

disappear entirely or wane perceptibly within several seconds. In performing the test the patient is first asked whether he is having his customary discomfort at that very moment. Then, when slowing has been produced by massage of the right or left carotid sinus, he is immediately asked whether the pain is worse. He is not asked whether it is better, as that would be a leading question. In fact, he is actually given a misleading question. If his reply is that the pain is gone or is letting up, the diagnosis of angina is fairly certain. If no significant slowing is obtained, no conclusion whatever can be drawn. The pain then may or may not be anginal. It is amazing how promptly the discomfort can be lessened by this maneuver. The pain may remain absent and that particular episode be over, or after a brief temporary relief it may return as the heart resumes its previous slightly rapid rate. I feel certain that the test may help in some cases to identify the coronary origin of discomforts in the chest before the condition takes on its more classic form, with its specific relations to effort. It has proved to be an additional diagnostic aid of practical use.

Among the errors prevalent at present is the ascribing of chest discomfort, otherwise characteristic of angina, to hiatus hernia because the gastrointestinal x-ray examination shows a small protrusion of the stomach through the diaphragm. Both conditions very frequently coexist where the stomach lesion proves to be an innocent and symptomless finding. There are occasions, however, when an acute episode of pain or distress with bleeding may be due entirely to a diaphragmatic hernia and the clinical picture resembles an acute coronary thrombosis. This possibility should always come to mind when an obese woman who is known never to have had hypertension develops an attack resembling a coronary thrombosis but shows no diagnostic changes in the electrocardiograms. The finding of blood in the stools may be very helpful in this differentiation.

Similar confusion may arise between gall-bladder and coronary disease. Here, also, the two conditions frequently are present in the same patient. The finding of gall-stones on x-ray studies proves that the patient has stones but does not mean that he is not also suffering from coronary disease. It is then necessary to appraise the symptoms carefully, ascribing to each its proper rôle in the production of the various symptoms. In some it will be decided that all the complaints are due to one or the other of the two possible causes. At times it may be decided that, although the patient may have been assumed to have angina, the heart is really entirely normal and all his trouble is biliary. In my own experience these are the only ones I have seen in which cholecystectomy has cured "angina." When I have seen such cases it really was clear preoperatively that they did not have angina, and it was therefore expected that the symptoms would vanish after gall-bladder surgery. However, when it was thought that both biliary and coronary disease were present I have never seen angina disappear after operation, though it might be improved. In this problem, as in others concerning the diagnosis of angina, the peculiar character of the symptoms and their

relation to effort and emotion and the other tests mentioned above, including the carotid sinus test, will all serve as guideposts in arriving at a correct diagnosis.

Another and in a sense a more important pitfall in the care of cardiacs is the distinction between acute coronary thrombosis and pulmonary embolism. At times this differentiation is extremely difficult. It is always very important because the latter may come and go, leaving the patient completely well, whereas the former always leads to a greater or less degree of concern. Furthermore, ligation of the femoral veins or Dicumarol anticoagulant therapy may be imperative and curative in cases of acute pulmonary embolism. It should be emphasized that changes in the electrocardiograms occur in both conditions, and those of one may be confused with those of the other. Occasionally there is a peculiar type of breathing with a sudden large pulmonary embolism. The patient seems to make quick gasps, lifting the clavicles and widening the mouth laterally, and yet the breath sounds are decreased. He appears to be making a considerable effort to get air but inhales very little, as if he had a foreign body in his throat. At times this feature has led to the correct diagnosis.

One word of caution is appropriate in this problem. When patients suffer some kind of collapse or severe episode after a traumatic injury, like a fractured bone, and it resembles an acute coronary thrombosis, the more likely diagnosis is apt to be a pulmonary embolism. The sequence of a traumatic accident, thrombophlebitis (whether detected or not) and pulmonary embolism is so frequent and logical that this diagnosis always deserves primary consideration. This decision may involve very important medico-legal matters, and in a few instances I have advised disinterring the bodies for postmortem examination months after burial, only to find that the original diagnosis of coronary thrombosis was incorrect and that death was due to pulmonary embolism. In these cases the widows readily obtained just compensation, as then there was no doubt that the accident was the direct cause of death.

There are many other conditions that may be confused with angina pectoris or coronary thrombosis. It is not the purpose of this discussion to analyze the various differential points, as they are almost endless. There are two features of acute dissection of the aorta that may deserve mention. It is well to obtain an x-ray of the aorta when the possibility of dissection arises and then to repeat this examination in a few days. At times a definite increase in the size of the aorta and an irregularity in its contour may establish the diagnosis of dissection of the aorta. A second point is a peculiar type of pain that occurs in a few of these cases. This consists of a severe, piercing pain in the back of the center of the throat radiating to the back of the neck. This peculiar localization of the pain is extremely rare in coronary artery disease. With a coronary attack pain is more likely to involve the lateral rather than the central aspect of the neck or jaw.

Now that operations on the valves of the heart have proved of value,

it not only becomes vital to make accurate anatomic diagnoses of valvular disease but it is also necessary to try to estimate the degree of stenosis or of insufficiency of the valve involved. The latter problem is the more difficult one. At present the main diagnostic challenge is the recognition of the presence of mitral stenosis and also of the amount of constriction, because operations on suitable cases of mitral stenosis have been so successful. The following features are those sought for to make the diagnosis: a diastolic and/or presystolic apical rumbling murmur, calcification of the mitral valve on fluoroscopy, an accentuated apical first heart sound, an opening snap (a third sound heard in early diastole at the apex), an accentuated and split pulmonary second sound, a broad, flat-topped and notched P wave in the conventional leads of the electrocardiogram, and evidence of right ventricular hypertrophy in the precordial leads, and, finally, x-ray evidence of a dilated left auricle and main pulmonary artery with right ventricular hypertrophy. A past history of rheumatic fever or chorea or the presence of auricular fibrillation may also indirectly aid in diagnosis. Needless to say, the presence of all these features is not necessary to establish the diagnosis. The detection of a calcified valve entails the least error. An apical murmur in some part of diastole is the most common and, in general, the most helpful diagnostic sign. The difficulty is that we now know that a small but significant number, among which are some that are most suitable for surgery, will show no diastolic murmur even on most careful auscultation. It is particularly in this exceptional group that all the other diagnostic criteria need most careful appraisal.

In trying to establish the diagnosis of organic heart disease there are only a limited number of reliable findings in the heart itself. Cardiac enlargement, a diastolic murmur, certain decidedly abnormal electrocardiograms or definitely abnormal x-ray findings may generally be accepted as evidence of organic heart disease. Systolic murmurs and almost all the various arrhythmias have been observed without any significant organic disease. To be sure, these benign features are also very frequently associated with serious disease as well. The important point is that other evidence of organic pathology is required before making a diagnosis of serious disease in cases showing slight systolic murmurs, transient or even permanent auricular fibrillation, and the like.

The second question, mentioned at the beginning of this discussion, is: When a patient is believed to have organic heart disease, is he also suffering from congestive heart failure? Hypertensive, valvular or coronary heart disease may be present for many years without failure and, in fact, congestive symptoms may never develop in some cases. It is idle to treat such individuals vigorously for years when they can do quite well without such treatment. One may be justified in outlining a program entailing mild prohibitions, but digitalis administration is likely to be useless and often makes the patient physically and mentally a little worse, unless one feels that moderate doses of foxglove delay the evil day of dilatation of the heart

and decompensation. The main point is that overtreatment of compensated cardiacs is a common error and results in more harm than good.

In trying to determine whether a known cardiac is actually suffering from congestive failure, it must be appreciated that examination of the heart itself tells us very little. Cardiac signs may reveal evidence of disease, but the only reliable sign of failure is the presence of a diastolic gallop. Murmurs, enlargement or arrhythmias aid in the diagnosis of a particular type of lesion but tell us nothing as to the state of compensation. For this purpose the history of unaccustomed dyspnea, either nocturnal or on effort, and the findings outside the heart are necessary. The difficulty is that the signs customarily indicative of congestive failure may be misleading. Edema of the legs may be due to nephritis, hypoproteinemia, varicose veins, lymph stasis, mechanical obstruction of the lower vena cava or large pelvic veins and other causes. An enlarged liver may be due to a neoplasm, cirrhosis, amyloid disease or other causes. Pulmonary râles or pleural fluid may be due to bronchitis, carcinoma, pneumonia and the like. Obviously the problems may be confusing.

When there is doubt in the mind of the physician whether actual congestive failure is present, the patient may require more elaborate study in a hospital for a few days. The finding of increased venous pressure in the arms is a fairly reliable sign of right-sided failure, unless there is some local venous obstruction. Similarly, a slowing of the velocity of blood flow (circulation time) is good evidence of left ventricular failure or pulmonary congestion. At times, the x-ray appearance of the lungs may be helpful in determining whether pulmonary congestion is present. Finally, the vital capacity of the lungs, which can be determined in one minute by any physician without trouble or expense to him or to the patient, can be a valuable guide to the presence or degree of left ventricular failure. It is very unlikely that a patient can be suffering from true cardiac dyspnea or can have significant left ventricular failure with a good normal or elevated vital capacity. However, this reading may be decreased in some thoracic condition other than heart failure, such as pulmonary fibrosis, emphysema, tumor, etc. In the latter conditions the circulation time will be normal. Although the earliest evidence of right or left ventricular failure is an elevation of end-diastolic pressure in these chambers or their respective auricles, catheterization studies of the heart are too elaborate to be used just to obtain this information, except in rare cases. In a word, laboratory studies may be necessary in some cardiacs to determine whether actual congestive failure is present.

The third important question to be asked is whether a known cardiac is suffering from some peculiar condition not likely to respond favorably to the orthodox program of treatment. There is an increasing group of cardiacs amenable to specific therapy medical or surgical. One may say that they make up the curable, or reversible, types of heart disease. It is imperative that these cases not be overlooked, for insofar as these factors

come into play in the causation of disability much help may be expected. Among the conditions should be mentioned beriberi heart disease, masked thyrocardiacs, constrictive pericarditis, some cases of severe anemia, congenital cardiac lesions that are operable (patent ductus, coarctation of aorta, tetralogy of Fallot, vascular ring, septal defects, etc.), arteriovenous aneurysm and, occasionally, an arrhythmia occurring in otherwise healthy hearts. This list of reversible types of heart disease will grow as further advances in our knowledge are made. But even now the situation presents a direct challenge to our profession, in that at least these curable conditions should be recognized and treated effectively.

It is helpful for each physician looking for slight clues that might lead to an accurate diagnosis to call to mind these various possibilities. As an illustration of this kind of approach, one should develop the routine habit of feeling for femoral pulses. If these are absent or very faint one must think of coarctation of the aorta. Here surgery may be curative. If the skin is warm, the pulse pressure increased, the diet quite inadequate and the alcoholic intake considerable, beriberi must be considered. Here thiamine therapy may restore complete compensation where digitalis is entirely ineffective. If the patient loses weight while eating well, prefers cold to warm weather, or has auricular fibrillation that fails to slow on full doses of digitalis, the possibility of thyrotoxicosis must be entertained. Here appropriate therapy may make anginal pain or congestive symptoms disappear completely.

Congestive failure, at times even of a severe degree, with cardiac enlargement, pulmonary congestion and hepatic engorgement, may occasionally result solely from an uncontrolled arrhythmia with a rapid heart rate. Auricular fibrillation or flutter and, rarely, ventricular tachycardia may develop in an otherwise healthy individual, and if the ventricular rate is rapid and remains so for a long enough time, the complete picture of severe congestive failure may result. I have seen such instances, in which restoration of a normal rhythm by the use of quinidine or Pronestyl has reëstablished complete compensation, with the disappearance of all signs and symptoms of heart disease. This possibility must be entertained if patients show these arrhythmias and there is no evidence of the common etiologic causes of heart failure, i.e., hypertension, coronary disease, rheumatic valvular disease or thyrotoxicosis.

Cases of constrictive pericarditis in older people are likely to be regarded as coronary sclerosis or chronic myocarditis in one form or another. This is not surprising when a man over 50 complains of weakness, breathlessness and vague discomfort in his chest, and shows some nondescript abnormalities in the electrocardiograms. Pericardial constriction should be suspected if the evidence of coronary disease is equivocal and there are some of the following signs: unduly increased venous pressure even after treatment for congestive failure, a diastolic thrust of the apex impulse, and striking suffusion of the face on assumption of the recumbent position. The latter

sign is observed in this condition and in cases of tricuspid stenosis. These features should be looked for, and then careful x-ray and fluoroscopy of the heart should be carried out in an effort to detect calcification of the pericardium or localized areas of decreased contractibility of the heart.

One could go on at great length with further illustrations, but it is sufficient to emphasize that these are the questions that must be asked and answered before one embarks on the customary treatment of cardiacs.

After the above three questions have been satisfactorily resolved, and the patient is found to have congestive heart failure without any of the reversible processes involved, he is then placed on a cardiac régime. This consists of appropriate digitalis, a low-salt diet, diuretics and rest. At the present time this plan of treatment is generally carried out quite satisfactorily by most physicians. The therapeutic pitfalls in current practice are not many.

One of the current difficulties in cardiac therapy when there has been no error in diagnosis is refractoriness to mercury diuretics. When congestive signs or symptoms fail to respond to intramuscular injections of mercury diuretics the physician must review the electrolyte status of the patient. Previous therapy, with frequent loss of large quantities of chlorides, may have produced a marked hypochloremia. Under these circumstances diuretics may fail completely to be effective. It will then be necessary to give large quantities of ammonium chloride, sometimes even intravenously, to restore a responsive state. At times the chloride in the blood may need to be elevated to a higher level than is customary for that patient before he will have a satisfactory diuresis from mercury injections. Furthermore, the potassium content of the blood and tissues may have become depleted from previous diuresis, and potassium chloride as well as ammonium chloride may be beneficial. Occasionally, in some cases with massive anasarca, mercury diuretics given intravenously (especially if followed by an intravenous injection of aminophylline) may initiate a diuresis that cannot be obtained by intramuscular injections. Also, if there is a great deal of ascites, the same diuretic which produced no diuresis *before* paracentesis may be effective *after* abdominal paracentesis. It would appear that the relief of pressure on the renal vessels permitted the diuretic to act. Another peculiarity of some of the more refractory cases of massive edema is that after the successful removal of a considerable amount of fluid from the legs by means of Southey's tubes, diuretics inert before this precedure may again become effective.

Other methods of therapy that are still being neglected are phlebotomy and thoracentesis. Many patients with congestive failure may be helped considerably by removal of a pint of blood. Nowadays, when most hospitals have blood banks, this procedure may have a double value. Whenever the cervical veins are distended and the venous pressure elevated, especially if hypotension is not present, this simple operation can cause striking improvement. In other cases the presence of a hydrothorax, particularly on the

right, is overlooked. At times even the removal of 500 c.c. of fluid will initiate a period of improvement in the patient's progress.

Some comments on digitalis are in order. With the current general use of the pure glycosides such as digitoxin and Digoxin, that seem to produce less nausea, many patients are over-digitalized. There has been a great increase in the incidence of digitalis intoxication in general practice. The toxic effect of digitalis is enhanced by potassium deficiency in the body cells. As a part of current cardiac therapy, with its low sodium intake and the frequent use of mercurial and other diuretics, many cardiacs are depleted of their body potassium and become more readily subject to digitalis intoxication on doses formerly nontoxic. One particular type of intoxication is so-called paroxysmal tachycardia with block. This peculiar arrhythmia, more common than is appreciated, results in a rapid heart rate with its inherent harmful effect. It may be mistaken for auricular tachycardia, auricular flutter or fibrillation, or possibly normal sinus tachycardia, and will be treated with further doses of digitalis. In point of fact, the drug should be omitted promptly and Pronestyl or potassium chloride administered, intravenously if necessary. The proper recognition and treatment of this peculiar complication of digitalis therapy may at times be life-saving.

Another matter of considerable importance is the question of bed-rest. A general misconception prevails in the minds of the medical profession concerning the value and indications of rest in bed. It has been assumed that the heart obtains maximal rest with the individual recumbent. This idea has become so imbedded in the minds of physicians and the lay public that if anything untoward happens to a patient while he is out of bed someone is thought to be blameworthy. On the other hand, all is forgiven if a patient is stricken with some catastrophic event or dies while in bed.

Since time immemorial patients have known that spells of suffocating breathlessness frequently occur during sleep in bed. Furthermore, such a spell would impel the patient to sit up in a chair or to even stand up and pace the floor to obtain relief. Only recently has it been proved by physiologic studies that recumbency increases blood volume and produces other deleterious effects on the circulation. In fact, within the past several months it has been shown by direct catheterization studies that the work of both the normal and the diseased heart is 23% greater in bed than with the patient in a chair with the feet down. It is evident from this that most cardiacs, including those with acute coronary thrombosis, are treated more effectively if kept in a comfortable chair with the feet down than if kept in bed all day. This is particularly true when dyspnea and pulmonary congestion are the main problems. The only contraindication to the chair method of treatment is when the patient is in a state of shock, or when lightheadedness or marked weakness make it too difficult for him to sit up. I am convinced that some fatalities could have been avoided if the patient had had the chair rather than the bed method of treatment.

Summary

The pitfalls in the care of cardiacs are numerous, but mainly concern the original diagnosis of the case. Before a physician embarks on the treatment of a given patient with heart disease he must ask himself three questions: First, is organic heart disease present? Second, is there evidence of congestive failure or coronary failure? Finally, is there something peculiar about the problem that requires more than the ordinary type of treatment, such as some form of surgical operation (pericardial resection), or is it a reversible form of heart disease, such as beriberi or thyrotoxic heart disease? Only after these three questions are satisfactorily answered should the patient be placed on the customary program of digitalis, diuretics, etc. When ordinary congestive heart failure is present, and the physician is certain that it is not due to one of the causes amenable to or curable by surgery, the problem is generally well treated by the average physician. Some of the difficulties and pitfalls in the treatment of congestive failure are discussed.

CASE REPORTS

ADDISONIAN CRISIS AND APPENDICITIS: A CASE REPORT*

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THE clinical picture of acute adrenal insufficiency may closely simulate that of acute abdominal inflammatory disease. The term "pseudoperitonitis" has been used to describe this syndrome.[3] Therefore, a differential diagnosis between Addisonian crisis and an acute abdominal inflammation can sometimes be very difficult.[3, 14]

Surgical procedures in cases of severe adrenal insufficiency are likely to lead to fatal results.[2, 8, 11] A careful examination for any manifestation of impending crisis is therefore indicated in every Addisonian patient with symptoms of acute abdominal disease. It is equally important in all persons with chronic abdominal pain for whom surgery is considered necessary to rule out chronic adrenal insufficiency, as various types of abdominal disturbances are not uncommon in this condition.[3, 14, 18] Repeatedly deaths have occurred after appendectomy for "chronic appendicitis" when autopsy has revealed destruction of the adrenal glands as the cause of the symptoms and the postoperative mortality.[6, 8, 11]

Acute or chronic appendicitis and adrenal insufficiency may occur simultaneously, in which instance an operation may precipitate the first overt manifestations of Addison's disease, or even Addisonian crisis.[4, 6, 7] This has long been considered a surgical catastrophe. Indeed, in reviewing the literature today we are able to find only one reported case of survival of the combination of acute appendicitis and Addisonian crisis, that of Leavitt in 1945.[7] On the other hand, Brezeau,[2] Dettre and Mera [8] and Laipply [6] have reported deaths under similar circumstances.

In patients with probable Addison's disease in whom elective surgery is contemplated, there is adequate time for the completion of studies which will exclude adrenal insufficiency. Acute abdominal emergencies, however, require immediate diagnostic and therapeutic measures. The difficulties involved in reaching a diagnosis and an interesting preoperative course are illustrated by the following case.

CASE REPORT

Admission Data: When admitted to the New York Medical College, Metropolitan Hospital Research Unit on September 29, 1953, the patient, a 29 year old white male, had already, during the preceding year, experienced three periods of extreme weakness, anorexia and loss of weight. For these complaints he had been previously

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hospitalized in July, 1952, and again in January, 1953. A tentative diagnosis of Addison's disease had been made. The patient had been treated with cortisone and "other" injections at irregular intervals.

On physical examination the patient was seen to be a well developed white male in no distress. He was 68 inches tall and weighed 125.5 pounds. There was diffuse brownish pigmentation of the skin, especially on the face. Points of pressure were not pigmented, and there was no increase in pigmentation of perineum or genitalia. Scattered bluish discoloration of the buccal mucous membrane was noted along both alveolar ridges. No abnormal findings were noted during the examination of the heart, lungs and other organs.

The blood pressure on admission was 110/70 mm. of Hg. The red, white and differential blood counts were normal. The fasting blood sugar and urea nitrogen were 55 and 14 mg. per 100 c.c., respectively. The serum sodium concentration on three consecutive days was 136, 130 and 132 mEq. per liter, respectively, and the corresponding values for chloride and potassium, 99, 98 and 94 mEq. and 5.0, 5.5 and 5.1 mEq. per liter, respectively. The 17-ketosteroid urinary excretion for the same three 24 hour periods were 5.1, 5.3 and 7.8 mg., respectively. An intravenously administered glucose tolerance test showed a high peak after one-half hour, and then dipped to slightly hypoglycemic values. A temporary glycosuria occurred at the peak of the curve. The Kepler-Robinson-Power test was positive for adrenal insufficiency with an equation (2) value of 20.

A salt-poor diet for three days resulted in very slight reduction in sodium chloride excretion. The administration of ACTH, 25 mg. on two successive days, was followed by decrease in the urinary excretion of 17-ketosteroids (from an average of 7.7 mg. to 4.6 mg.).

Clinical Course: The patient was maintained on an intake of 8 gm. of sodium chloride per day. In order to obtain basic values for the various laboratory tests, specific steroid therapy was at first withheld.

On the morning of October 24, during this pretreatment, the patient complained of nausea, abdominal pain and diarrhea. The pain had started at midnight and was localized in the right lower abdomen, the point of maximal intensity being at McBurney's point. The leukocyte count was 12,000 per cubic millimeter, with 65% neutrophils. The presence of acute appendicitis was indicated by the symptoms and physical findings, except that the temperature was only 98.3° F. (at 9:00 a.m.), and diarrhea rather than constipation was present. However, since the presence of Addison's disease had been proved, the question arose whether all his complaints could be caused by an Addisonian crisis.

At this juncture, after consultation between the endocrine and surgical services, a working diagnosis of acute adrenal insufficiency complicated by appendicitis was made and vigorous therapy instituted for the adrenal insufficiency, while further tests were done to confirm the presence or absence of inflammation.

By this time (11:00 a.m.) the blood pressure had dropped to 70/55 mm. of Hg and the temperature had risen to 101° F. Thirty cubic centimeters of aqueous adrenal cortical extract (ACE) were given intravenously. An infusion of 1,000 c.c. of 5% glucose in saline containing 20 c.c. of adrenal cortical extract and another infusion of 5% glucose in water containing 4 c.c. of Levophed were started. One hundred milligrams of cortisone and 5 mg. of DCA were given intramuscularly at noon, when the temperature was 102.5° F.

At 3:15 p.m., ACE, 30 c.c., was repeated intravenously, and another 1,000 c.c. of 5% glucose in saline containing 20 c.c. of ACE were given. The blood pressure had increased to 90/65 mm. of Hg; Levophed was discontinued at 4:00 p.m.

Again at 5:00 p.m., 30 c.c. of ACE intravenously and 500 c.c. of 5% glucose in saline containing 20 c.c. of ACE were given. At 7:30 p.m. the general appearance

of the patient had improved markedly. There was no further nausea. Local pain had ceased, but there was still some tenderness on deep pressure and on rectal examination. The patient was well oriented and euphoric. The leukocyte count had dropped from 12,000 to 10,000 without significant change in the percentage of neutrophils present. The temperature had dropped to 101° F.

Because of the persisting temperature, the continued right lower abdominal tenderness at McBurney's point and marked right-sided tenderness, a decision was made to operate in spite of the apparent improvement in the patient's general and localized condition.

Immediately prior to the operation the patient was given an additional 20 c.c. of ACE intravenously and 10 mg. of DCA intramuscularly. An infusion with 5% glucose in water containing 4 c.c. of Levophed was started.

Laparotomy was done under local anesthesia. When the abdominal cavity was opened an acute purulent appendicitis with a small perforation covered by the greater omentum was found. The appendix was removed and the incision closed *per primam*.

The postoperative course was completely uneventful. Postoperatively the patient was given 25 mg. of cortisone three times daily for two days, and 5 mg. of DCA three times daily for three days. Then the dosage of cortisone was lowered to 25 mg. twice daily, and DCA to 5 mg. at similar intervals. High dosages of penicillin and streptomycin were used. There was normal wound healing, and the general condition of the patient improved rapidly.

TABLE 1

Summary of Important Clinical Data in the Present Case

	Time 9 a.m.	Suggesting		Time 1 p.m.	Suggesting		Time 6 p.m.	Suggesting	
		Addisonian Crisis	Appendicitis		Addisonian Crisis	Appendicitis		Addisonian Crisis	Appendicitis
Nausea and vomiting	X*	+	+	0	+	−	0	+	−
Abdominal pain	X	+	+	X†	+	+	0	+	−
Tenderness at McBurney's point	X	−	+	X	−	+	X	−	+
Tenderness on rectal examination	X	−	+	X	−	+	X	−	+
Temperature	98.3°	−	+	102.5°	−	+	101°	−	+
White blood count	12000	−	+	Not done			10,000	+	−
Blood pressure	85/60	+	−	11 a.m. 70/55	+	−	90/65	+	−

* Denotes pain present.
† Pain present but decreased.

COMMENTS

Several régimes for proper preoperative and postoperative care of patients with acute adrenal insufficiency due to either Addison's disease or adrenalectomy have been suggested.[1, 14, 18] In all of these the administration of adequate amounts of fluids, electrolytes, adrenal cortical extract, DCA and 11-oxycorticoids is indicated. The most important of the steroid preparations used in such cases at the present time is either cortisone or hydrocortisone. The beneficial effects of cortisone in cases of chronic adrenal insufficiency have been described by Thorn.[17] The use of cortisone in acute adrenal failure after bilateral adrenalectomy has been very successful,[9] its main immediate effect probably being upon carbohydrate metabolism. The most rapid effect is obtained by the intravenous

administration of cortisone dissolved in propylene glycol. The simultaneous administration of DCA with large amounts of fluids and electrolytes provides adequate hydration and improves circulation. The described delaying effect of cortisone upon wound healing when given in high dosage and over an extended period of time [16] should not be a contraindication to its use in emergency operations in patients with acute adrenal insufficiency. The fibroblastic effect of DCA may lessen this action of cortisone.[13] As soon as the acute danger for the life of the patient is overcome, cortisone can quickly be reduced to doses which will not materially interfere with wound healing.[5]

Clinically, we want to stress the fact that the general condition of this patient and local manifestations of inflammation had markedly improved after the patient had obtained the above described medications and before surgery was carried out. There was even some euphoria, and the patient stated that he definitely felt better. The persistence of the local findings on careful examination, and the elevated temperature, were the indications which led to laparotomy. The improvement in the patient's condition in spite of purulent appendicitis with perforation and localized peritonitis was due to better hydration and improved metabolic and circulatory functions. The known stimulating effect of large doses of steroids upon mental status [15] may also have contributed to the sense of well being despite the progression of the abdominal condition. In similar cases, this must be kept in mind when the clinical picture is evaluated.

Summary

A case has been reported of the survival of a patient with Addison's disease who had simultaneously an acute adrenal insufficiency and perforated purulent appendicitis. The differential diagnosis was complicated by marked improvement of the general condition and local findings after active treatment for adrenal insufficiency. Preoperative preparation and postoperative care have been detailed.

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EPISODIC STOMACH CANCER*

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In this era of poor prognosis for stomach cancer we felt it would be encouraging to report the history of a patient who survived three separate stomach resections, each for carcinoma of the stomach. Little has been uncovered in this particular case which gives any insight into the mysteries of cancer; yet we feel that a collection of such peculiar case histories, in which a patient develops multiple tumors of an organ, may yield a common denominator in unraveling the riddle of individual susceptibility to cancer and individual resistance to such tumors once they appear.

The case seems worth reporting because we have been unable to find a similar case in our reading and because it is a case in point for major surgery in the aged.

Case Report

A 79 year old white man was admitted to the Baltimore City Hospitals on July 25, 1953, complaining of anorexia, sour eructations, weakness and weight loss. The patient had always suffered from sour belching and vomiting following the ingestion of heavy foods. In January, 1934, when he was 59, these symptoms became much worse, his appetite began to fail, and he began to vomit after every meal. He noticed

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that the vomitus was black and resembled coffee grounds. He noted no tarry stools, but he had lost 30 pounds.

Preoperative Findings: Examination at this time was not remarkable except for evidence of weight loss. The serologic test for syphilis was positive; the hematocrit was 47 per cent; the sedimentation rate was 24 mm. in an hour (Wintrobe method). Repeated fluoroscopic examinations of the stomach and large bowel failed to reveal any abnormality. Because there was gradual increase in vomiting he was admitted to The Johns Hopkins Hospital on July 15, 1934, with a diagnosis of partial intestinal obstruction, probably due to neoplasm of the lower bowel. Physical examination was again not remarkable except for evidence of weight loss. The erythrocyte count was 4.0 million, the hemoglobin 12.5 gm. per cent. A chest roentgenogram showed numerous areas of calcification in the right upper lobe, thought to be inactive tuberculosis. A barium meal on July 19 revealed a defect near the pylorus, thought to be a neoplasm.

First Operation: On July 23, 1934, through a right rectus incision, a small, well defined carcinoma of the pyloric end of the stomach was found. It was readily movable, and no metastases to lymph nodes or liver were seen. A Billroth II resection was carried out without difficulty.

Pathology Report: On opening the resected specimen a crater-like depression with rolled, overhanging, hard margins was found at the pylorus. The crater was about 4 cm. in diameter. Microscopic examination showed a well differentiated adenocarcinoma of the pylorus at the margin of the crater. No lymph nodes were involved.

Postoperative Course: Following operation, the patient was seen in the Gastroenterology and Syphilis Clinics, where he received adequate heavy metal therapy for the syphilis. He continued to return to the clinic on an average of once monthly between 1936 and 1946.

On January 11, 1946, the patient was admitted to the Medical Service of The Johns Hopkins Hospital for the second time with the complaints of cough, chest pain and dyspnea of 10 days' duration. He had noted feverishness and had coughed up small amounts of dark brown sputum.

Preoperative Findings: Physical examination showed a temperature of 102.2° F., a pulse rate of 100, respirations of 32, and a blood pressure of 110/60 mm. Hg. There were signs of consolidation over the right lower lobe. Otherwise the examination was within normal limits.

The leukocyte count was 15,000; the erythrocytes were 2.3 million; hemoglobin was 7 gm. %, and hematocrit was 20 %. The sputum yielded types 19 and 20 pneumococcus. The urine was normal, and the stool was negative for blood in repeated examinations. There was no free acid in the gastric contents after histamine. The serologic test for syphilis was positive.

A chest roentgenogram showed a recent infiltration in the right lower lobe in addition to the old calcifications. A diagnosis of pneumococcal pneumonia was made and the patient was treated with penicillin, with rapid clearing of signs and x-ray findings.

In an attempt to find the cause of the patient's anemia, an upper gastrointestinal series showed a large mass in the lumen of the stomach. Gastroscopy revealed a small, bleeding, cauliflower-like growth.

Second Operation: The patient was transfused, and on March 1, 1946, he was explored operatively through the previous incision. A hard tumor the size of a golf ball was felt in the posterior portion of the stomach near the old anastomosis. A portion of the jejunum around the anastomosis, the omentum and a portion of the transverse colon were removed, along with two thirds of the remaining stomach. The ends of the jejunum were anastomosed end-to-side by the Roux technic, and

the stomach was closed by the Hofmeister technic. The transverse colon was sutured end-to-end. No metastases were felt, but several suspicious lymph nodes along the posterior surface of the stomach were sent for section. A small polyp was found in the stomach at the site of the anastomosis and was also sent for section.

Pathologic Report: On opening the specimen the pathologist noted a large, cauliflower-like mass measuring 5 cm. in diameter and 2 cm. in height just above the old anastomosis. The surrounding mucosa was not infiltrated. Underneath the tumor a large, discrete lymph node on gross section appeared to be replaced by tumor.

Microscopically, the stomach lesion was an adenocarcinoma. Only the large lymph node near this lesion showed metastases.

Postoperative Course: The patient had a slow but uneventful postoperative course and was discharged March 28, 1946. During the interval from 1946 to 1952 the patient was asymptomatic and kept none of his clinic appointments.

Preoperative Course: For one year before the present admission, in June, 1953, he experienced a recurrence of his former symptoms, viz., anorexia, sour eructations, weakness and a 22 pound weight loss. He weighed 103 pounds but did not appear wasted for a man of 79 years. Except for abdominal scars from previous operations, the remainder of the examination was normal.

The stool contained no gross or occult blood. The erythrocyte count was 3.5 million mm.^{3}, the hemoglobin 12 gm. %. A barium meal resulted in a normal x-ray study in July, 1953. Because of the man's past history and his persistent symptoms, another stomach x-ray study was performed in September, 1953, which then showed a large filling defect in the fundus of the remaining stomach. Gastroscopic examination was technically unsuccessful. Since there was no evidence of metastasis, and the patient was in good condition despite his 79 years, another abdominal exploration was recommended.

Third Operation: On November, 1953, a 7.5 cm. wide, fungating lesion was removed together with the remainder of the stomach by block dissection including a portion of the pancreas to which the tumor was adherent, the spleen and greater omentum.

Pathology Report: Microscopically, the lesion was a medullary carcinoma. Several lymph nodes were involved with metastasis.

Postoperative Course: The postoperative course was uncomplicated except that the patient is suffering from annoying, but not debilitating, postprandial diarrhea. However, he has gained 14 pounds up to preoperative levels.

Comment

Because the etiology of cancer is unknown to date, it remains a mysterious disease. The natural history of cancer, however, seems to correspond to that of other pathologic processes. This case fits in nicely to complete the life cycle of malignant disease, making it similar to the life cycle of other, better defined diseases. The life cycle of many diseases with which we are familiar includes a latent period which is subclinical, an acute stage, an intermittent or episodic stage with exacerbations and remissions, and a chronic stage—and so it is with cancer. Of course, depending on the severity of the disease and the host resistance, any of these stages may end fatally.

Cancer as a chronic disease has been well described by Morton.[1] This author has collected 17 cases of cancer of many varieties in which the patients lived useful lives with an active malignancy. Even more unusual are the patients whose cancers become quiescent after years with no treatment. When cancer behaves in this manner, it is behaving not unlike the rare cases of chronic glo-

merulonephritis which Keith described [2] who have recovered with no clinical residue.

To find clinical examples of cancer in the latent or intermittent stages is not as easy. Yet we are all familiar with cancer as an acute disease, particularly stomach cancer. The patient usually presents himself with symptoms of short duration. Upon surgical exploration, a small intragastric lesion may be found with widespread metastasis. True, the duration of this type of cancer is probably longer than that of most diseases which we normally call acute processes; yet in comparing it to the longer clinical course of most cancers, it is an acute course.

Talks with experienced surgeons and a search of the medical literature yield several examples of cancer in its latent phase. A good example of this type is a case reported by Dr. Finney, whose father resected an adenocarcinoma of the stomach in a patient who 17 years later died of tuberculosis.[1] At autopsy, six lymph nodes under the diaphragm were found to contain adenocarcinoma. These nodes caused no symptoms and presumably represented latent cancer. Included in this group of latent cancer are those patients who seem to have had a complete excision of their cancers but several years later reappear with metastasis from the original lesion. Apparently, lymph nodes and other tissues occasionally are able to contain the rapid growth of cancer, rendering the disease clinically dormant for an indefinite time. Unfortunately, this inactive cancer focus may become suddenly activated, just like an inactive tuberculous focus. For best results, these latent foci should be eradicated. Wangensteen [3] attempts to treat these foci by a re-operation six months after the first procedure, which he calls his "second look." While we do not have his results with this approach, he has certainly introduced an important idea in his attempt to cope with the latent, but deadly, foci of cancer unavoidably left behind because they are not grossly visible to the surgeon.

The case we are reporting falls into the intermittent or episodic form of cancer. This disease type, of course, is more characteristic of the inflammatory process, with its acute exacerbations and remissions, than it is of a malignant growth. The obvious reason for this is that cancer, in its initial attack, more often than not terminates fatally.

We are purposely avoiding the argument as to whether any of the cancers were related, because this is not answerable. At any rate, the patient was well for 12 years after his first localized cancer was resected by subtotal gastrectomy. This is not unusual because, as Wangensteen points out, 50 to 60% of patients without lymph node metastases survive five years or more. At his second operation this patient had lymph node metastasis, yet did well for seven more years postoperatively. This is more unusual, since the chances of five year survival with cancer of the stomach and lymph node metastases are only 10 to 11%. At the last operation he again had lymph node metastases.

Summary

In summary, this patient had a peculiar susceptibility to stomach cancer, which developed on three different occasions. At the same time, he seems also to have an above-average resistance to the spread of these cancers and this has enabled the surgeons so far to resect the tumors successfully.

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NONPARASITIC CYSTIC DISEASE OF THE LIVER*

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ALTHOUGH non-parasitic cystic disease of the liver is a comparatively rare pathologic entity, it is encountered with sufficient frequency that the internist should certainly be aware of its manifestations. From a review of the literature it would appear that this condition can make itself evident at any period of life. Witzel [1] and Sanger and Klopp [1] in 1880 reported cases of large solitary cysts of the liver found in fetuses which, in both instances, were of such a size as to complicate delivery of the child. Bagot [2] in 1892 reported a similar case of a liver cyst containing 2½ gallons of fluid and complicating delivery. At the other extreme of life we find the oldest case in the literature reported in a patient of 82 by McCaughan and Rassieur.[4] These last authors analyzed 80 cases and found the average age at diagnosis to be 33 years. Beattie and Robertson [5] reviewed 62 cases and found that the diagnosis was made most commonly between the fourth and sixth decades. The female sex appears to have some predisposition to this condition. Various authors quote the incidence as varying between 3:1 and 4:1 of females over males.

Heredity seems to play some part in certain instances. In a case of congenital polycystic disease of the kidney and liver reported by Campbell,[6] two siblings of the patient were definitely known to have had cystic kidneys. Other congenital malformations, such as spina bifida, meningocele, polydactylism, vesical anomalies and hypospadias, have been found in association with cases of cystic liver disease.

The concurrence of cystic disease of the liver and cystic disease of other organs, particularly the kidney, is well known and has been commented upon by several authors. Moschcowitz [1] reviewed 85 cases of cystic disease of the liver and found that in only 10 of these cases was the liver alone affected. In 19%

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of polycystic kidneys he found the liver also showed cysts. Davis[8] in 1937, in a review of 499 cases of cysts of the liver, found that 152 of these had kidney cysts as well. Cystic disease of the liver has also been found in a few instances in conjunction with cystic disease of the pancreas, spleen, ovaries, lungs, brain, pituitary, breast and peritoneum. Ackman and Rhea[9] found 11 of non-parasitic cysts of the liver in 6,141 necropsies at the Montreal Hospital. Eliason and Smith[10] found 88 cases in 20,000 necropsies at the Philadelphia General Hospital. Two cases in 211,046 admissions at the same hospital were diagnosed ante mortem and only one preoperatively.

Pathologic Features

Non-parasitic cystic disease of the liver can be said, in general, to assume two essential forms, the solitary or the multiple. Some authors have attempted to differentiate one from the other as to etiology. However, we feel, like most, that this is impossible, since the walls of many of the described solitary cysts show trabeculations which could indicate a multilocular origin.

Solitary cysts may achieve tremendous size, as in the case of Parry,[11] where the cyst extended into the pelvis and was the size of a full term pregnancy. Such cysts are mostly pedunculated, but at times they may be entirely intrahepatic, as in the case of Eliason and Smith,[10] where the entire right lobe of the liver was involved and destroyed. Solitary cysts are most commonly found at the antero-inferior portion of the right lobe of the liver.

Multiple cysts may be found limited to one of the lobes, or they may involve the whole liver. The distribution has been analyzed as follows:[8] 499 cases were described, 187 being solitary, 20 solitary monolocular, and 241 multiple and 51 not stated. Out of 62 cases;[5] the right lobe was involved in 20 cases, the left lobe in 10 cases, the quadrate lobe in one case, both lobes were involved in six cases, in 9 cases it was impossible to state at operation from which lobe the cyst arose, and in 16 cases the location of the cyst was not stated by the author.

In contradistinction to echinococcus cysts, nonparasitic cysts have a low internal tension. The external surface is usually smooth, glistening and grayish blue, often showing many dilated veins, their external appearance being not unlike that of a smooth-walled ovarian cyst; the internal surface is usually smooth, less regular, and often translucent. The thickness of the wall is variable and usually shows no definite line of cleavage between the wall and the normal liver tissue. This wall appears microscopically to consist of three layers: an internal layer, rich in cellular elements, usually lined by cuboidal or columnar epithelium; a middle, dense layer, poor in cellular nuclei and containing a few blood vessels with thickened walls; and a loose outer layer, with elastic connective tissue fibers, muscle bundles rich in cells, and many blood vessels and bile ducts.

The cysts contain variable amounts of fluid, which may be clear, serous, yellow or brown, thin or viscous. Albumin is always present; bile and bile pigment are generally absent, but may be found in some cases. The specific gravity has been stated[9] to vary between 1.007 and 1.024. Microscopic examination of the contents may reveal fat droplets, fatty acid crystals, cholesterol crystals, hematoidin crystals, leukocytes, red blood cells and even fibrin.

Etiology

The etiology of this condition is not definitely established. The reader is referred to the excellent article by Toland,[2] in which the various interesting hypotheses are very adequately reviewed. The most popular etiologic classification is that of Jones:[7] (1) teratomatous or embryomatous cyst; (2) pseudocyst; (3) lymphatic cyst; (4) cystic degeneration of liver with polycystic kidneys; (5) cysts that arise from blood vessels; (6) cystadenomata; (7) ciliated epithelial cysts, and (8) retention cysts.

Clinical Signs And Symptoms

The great majority of the reported cases reveal that these cysts usually give rise to no symptoms and are discovered merely by reason of their size. However, symptoms may be present and they are usually due to pressure upon neighboring organs, hemorrhage into a cyst, torsion of its pedicle, inflammation, and rupture. Frequently the symptoms are secondary to those due to associated polycystic kidney disease. Pain in the right upper quadrant of the abdomen or in the epigastrium is frequently described. Nausea and vomiting secondary to pressure upon the stomach or duodenum are often seen. Jaundice has been only occasionally encountered, and then it has been felt to be due to pressure of the mass upon the common bile duct.

In those cases where rupture occurs, signs of peritoneal irritation will be found. Commonly the cysts have been mistaken for other clinical conditions, such as hydrops of the gall-bladder, ovarian tumors or mesenteric, renal or pancreatic cysts, and the correct diagnosis was achieved only at the time of surgery. Hoffmann[9] has called attention to the fact that the mobility of the cyst in a downward direction is limited by its attachment to the liver when the cyst is pedunculated, while lateral mobility is quite free.

Treatment

The treatment of this disease appears to be entirely surgical. The following procedures have been performed: (1) aspiration, (2) incision and drainage, (3) marsupialization, (4) partial or complete excision, and (5) anastomosis of the cyst to the small bowel. Of 226 cases which came to operation, 50 died (a 22%[8] mortality rate).

The following case presents some of the usual problems encountered in this condition. It is of special interest in that x-ray studies of the upper gastrointestinal tract and gall-bladder demonstrated the presence of an extrinsic pressure defect produced by one of the cysts. We believe this is the first time this type of a defect has been demonstrated; its presence gave us a clue which, together with the clinical findings, made possible the achievement of a correct preoperative diagnosis.

Case Report

The patient was a 62 year old white female civilian dependent admitted to Fitzsimons Army Hospital on May 14, 1952, with the chief complaint of right upper quadrant pain of four years' duration. The patient described this pain as being colicky in character, and stated that it had become more severe during the previous

year. She had noted that it would radiate around the right costal margin up to the region of the right scapula. She stated that she had definitely noticed that fatty foods would bring on attacks of bloating and right upper quadrant discomfort.

There was no history of jaundice, chills, fever or stools of abnormal color. On occasion the patient would be awakened from sleep by her discomfort, and she stated that at the climax of the colicky pain it felt "as though someone was pushing his heel into my side." Because of these symptoms, the patient came to the Out-Patient Clinic at Fitzsimons Army Hospital and was from there admitted to the hospital.

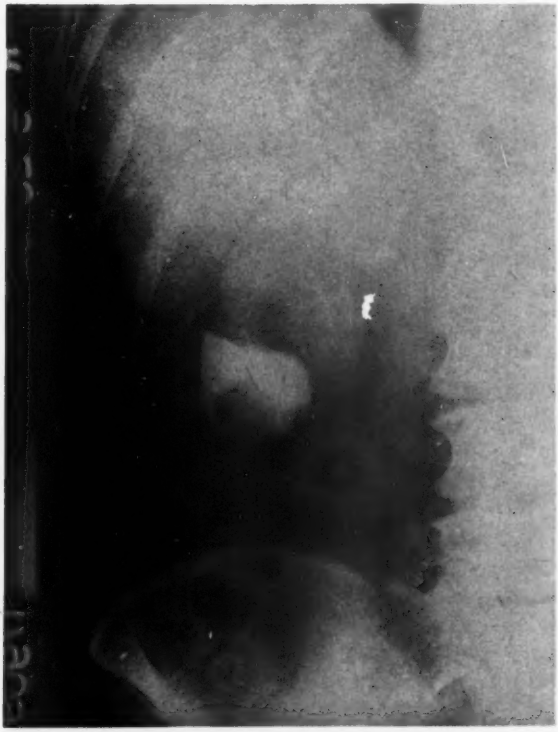

FIG. 1. Pressure defect on the gall-bladder by the liver cysts as demonstrated by gall-bladder series.

Her family history was essentially negative. Patient had given birth to 19 children, 14 of whom were living, the others having died in infancy or at birth of causes unknown.

Systemic review revealed that the patient had had some gynecologic difficulties in 1935, and that she had been operated on at that time for leiomyomata of the uterus. At the time of operation it was noted that she had several cysts arising from the substance of the liver, and two of these were removed. We were able to make contact with the surgeon who did the operation in 1935, and according to his records a diagnosis of cystic disease of the liver had been made at that time.

Physical examination revealed a rather obese, well developed and well nourished 62 year old white female who did not appear to be in acute or chronic distress. Temperature was 98.6° F.; pulse, 80; blood pressure, 150/90 mm. of Hg. Examination of the abdomen revealed moderate tenderness to deep palpation in the right upper quadrant, and in this same region a palpable mass was present. The mass was the size of an orange, relatively soft, and gave the impression of being cystic. It appeared to be attached to the liver, descending with this organ during inspiration. The remainder of the physical examination was entirely negative.

Laboratory data revealed a normal hemogram. Fasting blood sugar varied between 134 and 152 mg. %. Liver function tests revealed a serum bilirubin of 0.1 mg. %; thymol turbidity, 1 unit; cephalin flocculation, normal; normal alkaline

FIG. 2. Pressure defect on both the duodenal bulb and the gall-bladder as shown by simultaneous gall-bladder and upper gastrointestinal series.

phosphatase; 4.5% Bromsulphalein retention; cholesterol, 225 mg. %, with ester partition 80% of the total. Serologic test for syphilis was negative.

X-ray Findings: A gall-bladder series revealed an extrinsic pressure defect across the body of the gall-bladder (figure 1). When barium was given by mouth and a combined study performed a semilunar filling defect was revealed across the superior border of the duodenal bulb continuous with the defect on the gall-bladder (figures 2 and 3). Routine chest films were negative except for moderate fibrosis throughout both lung fields. There were also flattening of both leaves of the diaphragm and blunting of the costophrenic angle. The aortic knob was prominent; the size and contour of the heart were within normal limits. A barium enema and two intravenous pyelograms were normal.

Course in the Hospital: Patient was felt to be a mild diabetic who was easily controlled on diet alone. Because of the x-ray findings and the clinical symptoms

it was felt that the patient should be explored operatively to establish a definite diagnosis and to relieve her of her pain. This was done on July 1, 1952, by one of us (N. J. C.). At the time of surgery a very large number of cysts was noted to be present scattered throughout the substance of the liver. Palpation of both kidneys failed to reveal any cysts. Four of these cysts were excised and adhesions from one of these to the duodenum were freed. Since nothing else could be accomplished for the patient because of the extreme dissemination of her disease, the operation was terminated at this point. The postoperative course was uneventful. A 15 cm. Penrose

FIG. 3. Pressure defect on the duodenal bulb by the liver cysts.

drain remained in place for 26 days postoperatively, and was gradually removed by traction.

PATHOLOGIC REPORT

The specimen consisted of four thin-walled cysts of varying size (figure 4), the smallest measuring 0.7 cm. in diameter. One segment was composed of two cysts and a small fragment of liver tissue, the cysts measuring 2.7 and 4 cm. in diameter, respectively. The wedge of liver tissue joining these cysts measured 4.5 by 2.2 by 1.4 cm. A second mass consisted of a single cyst measuring 9.5 cm. in diameter. The third surgical specimen was that of a 1 cm. cyst which included an 0.8 cm. cyst in its

wall. The largest cyst received was covered over half of its surface by a 9 cm., roughly circular disc of omentum.

Incision into the cysts revealed that the two larger cysts were filled with cloudy yellow fluid which appeared to contain a considerable quantity of fat, and the two cysts that were attached to one segment of the liver tissue were filled with clear, straw-colored fluid. Representative sections were taken and the fluid was examined for echinococcus, with negative results.

Microscopic Examination: Slides showed cysts incompletely lined by a single layer of thin columnar cells showing focal areas of flattening to low cuboidal and even squamous forms (figures 5 and 6). In some areas the epithelium was absent,

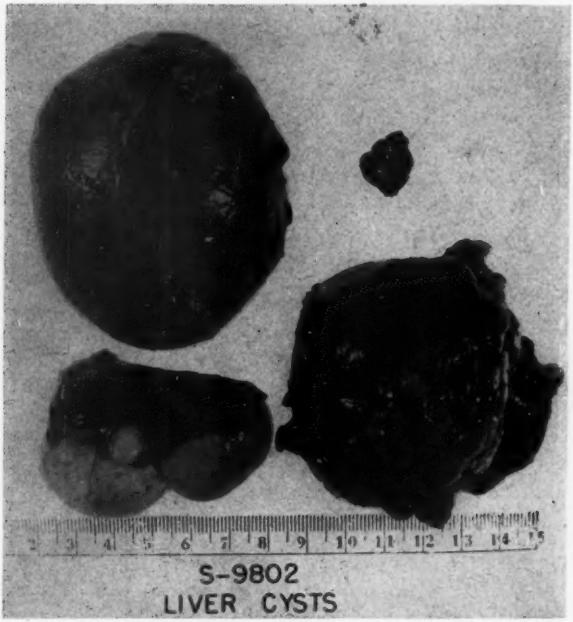

FIG. 4. The four cysts which were removed in an effort to relieve the pressure exerted by them on the surrounding structures.

and a few macrophages with foamy cytoplasm were found in direct contact with the fibrous tissue wall.

Liver tissue surrounding the cyst showed collapse of the lobules, with degeneration of the parenchymal cells. There was a pink layer of fibrous tissue immediately beneath the cyst lining. The fibrous wall contained a moderate number of plasma cells and lymphocytes and numerous bile ducts of various sizes, some of which showed a moderate amount of dilatation. The liver tissue beyond the cyst wall showed normal architecture, and there was no suggestion whatsoever of malignancy. Diagnosis: biliary papillary cystadenomatosis of the liver.

Following an uneventful postoperative course, the patient was discharged from the hospital and has remained asymptomatic to this time.

FIG. 5. Photomicrograph showing the columnar and cuboidal epithelium lining the cysts. Note the fibrosis and chronic inflammatory reaction in the area of destroyed liver tissue surrounding the cyst.

FIG. 6. Photomicrograph showing an area of squamous and cuboidal epithelium lining one of the cysts.

SUMMARY

1. A review of the literature on nonparasitic cystic disease of the liver is presented, with enumeration of clinical and pathologic findings.

2. A case in point is presented featuring the clinical, surgical and pathologic features, with illustrations of the x-ray, gross and microscopic features of this particular case.

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EOSINOPHILIC GRANULOMA OF FEMUR AND LUNGS: A CASE REPORT *

By JOHN H. CHILDERS, M.D., JOHN W. MIDDLETON, M.D., F.A.C.P., and MARTIN SCHNEIDER, M.D., *Galveston, Texas*

EOSINOPHILIC granuloma of bone was described by Otoni and Ehrlich [1] in 1940 and was referred to as "solitary granuloma of bone simulating primary neoplasm." Lichtenstein and Jaffe [2] described this entity practically simultaneously, and first applied the term "eosinophilic granuloma." Farber,[3] Green and Farber [4] and Mallory [5] pointed out that solitary or eosinophilic granuloma of bone was but one of related disorders referred to as Hand-Schüller-Christian and Letterer-Siwe disease. The differential features of these lesions depend largely upon the tissues involved.

Currens [6] recorded a case of Hand-Schüller-Christian disease with a defect in the right parietal region of the skull and with radiologic evidence of bilateral pulmonary fibrosis. Roentgen treatment of the calvarium and chest

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resulted in alleviation of the clinical symptoms. Subsequently Engelbreth-Holm et al.[7] studied a five year old boy with skull and pulmonary lesions who developed diabetes insipidus and the classic picture of Hand-Schüller-Christian disease one year after initial examination. Additional cases of eosinophilic granuloma of bone associated with radiologic evidence of pulmonary lesions have been described by Arnold,[8] Weinstein,[9] Ackerman,[10] Dickson,[11] Quintana,[12] Kruger,[13] Parkinson[14] and Adams.[15] No postmortem studies had been recorded, until Farinacci et al.[16] described for the first time the pathologic changes occurring in the lungs. In 1951 Brody[17] reviewed 15 cases of eosinophilic granuloma of bone with pulmonary lesions and reported one additional case. Three additional cases of eosinophilic granuloma of the lungs were reported in 1954 by May et al.[18] Two of these cases had simultaneous osseous lesions and pulmonary lesions that were studied histologically. We have had the opportunity to study one case of eosinophilic granuloma of bone and of lung in which both lesions were diagnosed after tissue had been excised for biopsy. These findings, the therapeutic response and the follow-up studies constitute the basis for this report.

Case Report

The patient, a 24 year old white male, was admitted to the University Hospital on April 20, 1952.

Chief Complaint: Shortness of breath, cough and weakness.

Present Illness: Since the patient entered the Navy in 1945 he had had frequent "colds" and almost continuous "bronchitis," with an intermittent cough producing a small quantity of sputum but no blood. The symptoms had been intensified during the preceding eight months, with progressive exertional dyspnea, more frequent and more productive cough, retrosternal pain at the height of inspiration, and occasional night sweats with fever of 101° F. (by mouth) but no chills. There had been a moderate weight loss (10 pounds). The patient had been treated by his physician with a regimen of vitamins and antibiotics, without improvement. X-ray examination of the chest revealed bilateral pulmonary disease interpreted as tuberculosis. Sputum examinations for acid-fast bacilli were negative. After his referral to one of us (J. M.), repeated sputum examinations were again negative, as were intradermal skin tests with old tuberculin 1: 10, coccidioidin and histoplasmin. A series of roentgenograms of the chest had revealed in the meantime a gradual progression of the bilateral pulmonary disease.

Occupational History: Since discharge from military service the patient had worked as a chemist for a petroleum corporation in a chemistry laboratory. His job required very little physical effort, and he had been working until the time of hospitalization here. There was rarely exposure to so-called "fluid catalyst," a finely powdered aluminum silicate.

Family History: Noncontributory except for history of tuberculosis contact with maternal grandmother and one aunt when he was about three months old.

Past History: No unusual or serious illnesses other than "cat fever" when in the Navy. No significant injuries or operations. He had passed through areas of endemic coccidioidomycosis in California about six times; there had been no previous symptoms attributable to this exposure.

Review of Systems: The only significant history is detailed in the present illness, above.

Physical Examination: Blood pressure, 126/72 mm. of Hg; temperature, 99° F.; pulse rate, 76 per minute; respirations, 24 per minute. The patient was a well developed and fairly well nourished white male. His appearance was compatible

with the stated age of 24 years. He appeared chronically ill and somewhat anxious, but in no acute distress; he was well oriented and coöperative. There were no physical findings of significance; the chest examination on several occasions showed a surprising lack of positive findings.

Laboratory Examination: Blood count and urinalysis were not remarkable. Serologic and skin testing had been carried out prior to admission to the hospital and were negative. On December 13, 1951, the erythrocyte count was 4,480,000; hemoglobin, 12.8 gm.; leukocyte count, 8,500, with a differential count of 6% stab forms, 67% segmented neutrophils, 25% lymphocytes and 2% eosinophils.

Roentgenographic Examinations: A series of films was obtained from outside sources and revealed the following findings:

A 4 by 5 inch survey chest film dated February 20, 1950, revealed findings compatible with a normal adult chest and no evidence of pulmonary abnormality (figure 1).

Chest x-ray examination in January, 1952, when the patient was first seen by his physician, showed bilateral interstitial pulmonary infiltrations with areas of small nodulation in the upper lobes and diffusely distributed small rarefactions representing alveolar emphysema. There was some coalescence of the inflammatory disease in each upper lobe; the posterior basal segments of the lower lobes seemed least affected by this disease process. There was absence of mediastinal and hilar lymphadenopathy. The cardiovascular silhouette appeared normal. The diaphragm was smooth, and the

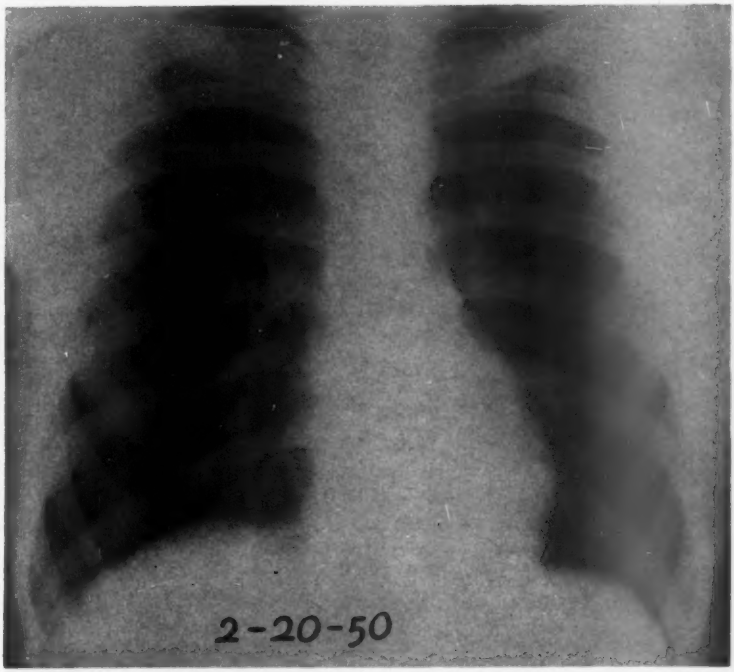

FIG. 1. February 20, 1950: Chest survey film (4 × 5 in.) at time of employment reveals no evidence of pathologic change in the thorax. The lung fields show normal bronchovascular pattern and normal aeration.

costophrenic angles were acute. There was no evidence of involvement of the bony framework of the chest. These findings appeared to represent a diffuse interstitial pneumonitis with bronchiolitis and alveolar emphysema, etiology undetermined (figure 2).

Further roentgen examinations up to the time of chest surgery revealed slight progression of these findings, without change in their character but with increase in coalescence of the upper lobe infiltrations.

Course in Hospital: After the patient's admittance to the hospital a right exploratory thoracotomy was performed on April 23, 1952, by Dr. A. W. Harrison, and

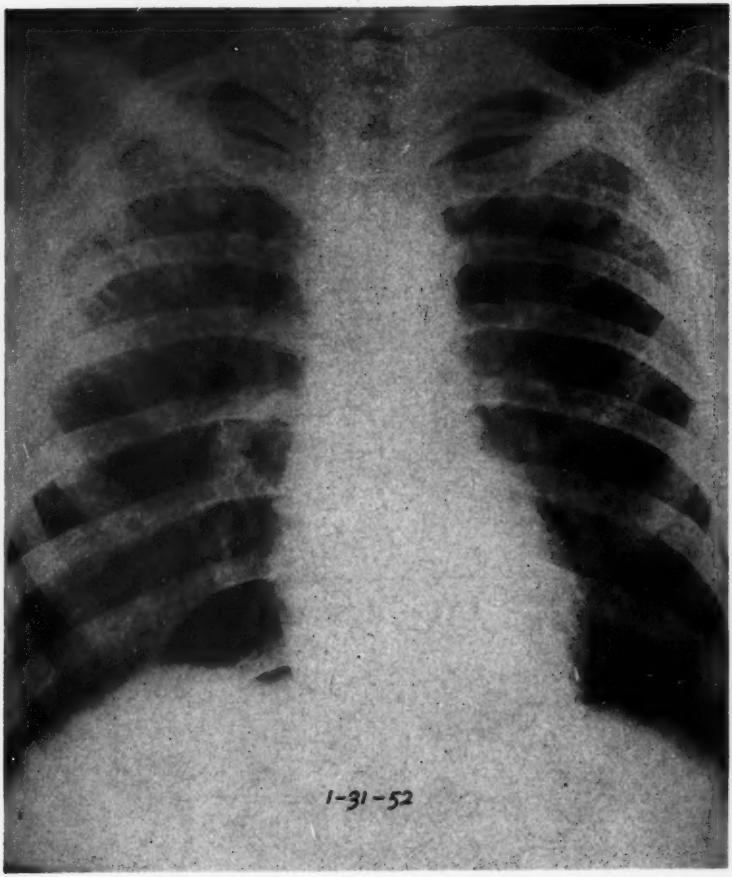

FIG. 2. January 31, 1952: Chest roentgenogram reveals bilateral interstitial infiltrations in the lungs, with slight coalescence in patches in each upper lobe and innumerable alveolar emphysematous blebs. There is no evidence of hilar or mediastinal lymphadenopathy, pleural effusion or cardiac change, or of involvement of the visible bone structures or diaphragm.

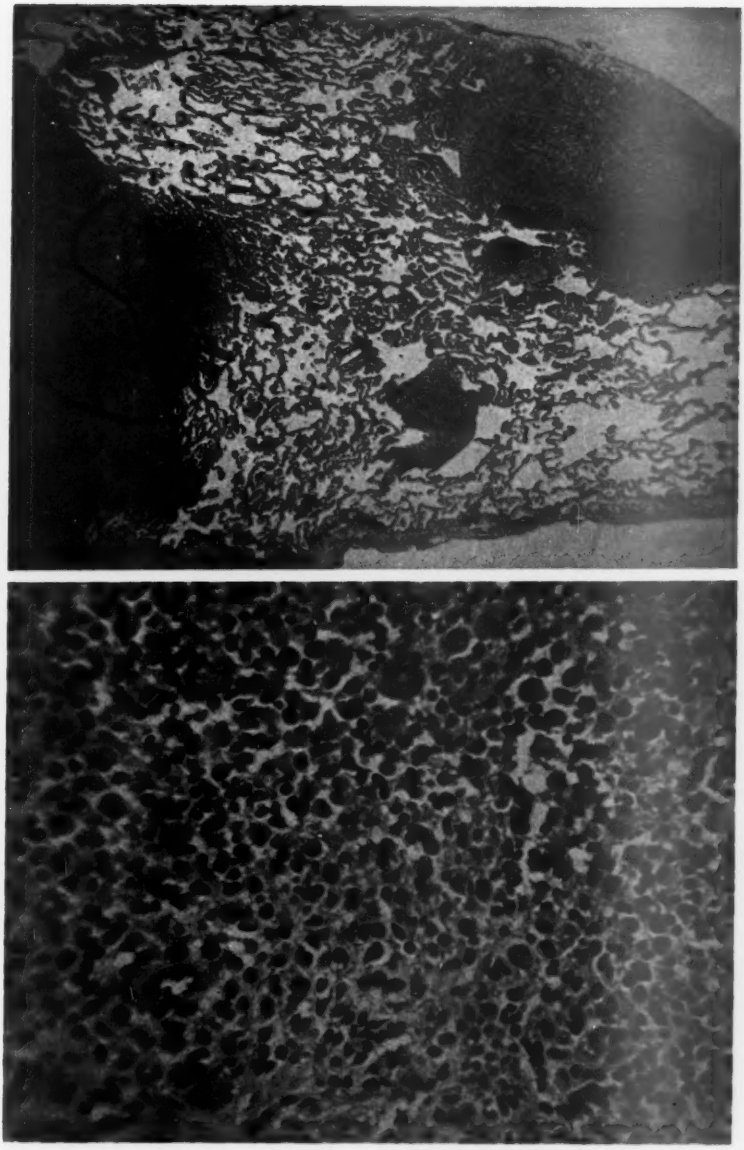

FIG. 3. (*above*) Focal nature of pulmonary lesions is shown with subpleural fibrosis. Hematoxylin and eosin. × 30.

FIG. 4. (*below*) The numerous histiocytes were associated with an occasional multinucleated form. Small vascular spaces course through the central portion of the nodule. H. and E. × 240.

lung tissue was removed for biopsy. Direct visualization of the pleura and lung revealed dense adhesions over most of the upper half of the right upper lobe. Under the visceral pleura on all surfaces, most concentrated in the superior segments of the upper lobe, there were discrete, hard, grayish yellow nodules, 2 to 10 mm. in diameter, which tended to be confluent in the upper portions of the right upper lobe. There were no lesions on the diaphragm, pericardium or parietal pleura. There was no evidence of necrosis.

Histopathology: Microscopic sections of the triangular portion of pulmonary parenchyma showed subpleural and interstitial focal collections of eosinophils and large mononuclear cells (figure 3). Fibroblastic proliferation was most marked in the margins adjacent to the visceral pleura. The central portions of the lesions were composed predominantly of histiocytes. An occasional multinucleated histiocyte was noted (figure 4). These large cells presented a faintly eosinophilic-staining cytoplasm containing a few small vacuoles. No sudanotropic material was identified within these cells when stained with appropriate reagents. Periodic acid-Schiff staining method revealed no specific etiologic agent. Numerous small blood vessels coursed through the involved areas, but no evidence of remaining pulmonary architecture was detected in the hematoxylin- and eosin-stained sections or with special stains. The eosinophils were most numerous at the periphery of the nodules. Many of the nuclei of the eosinophils contained two segments. Compressed alveolar spaces at the periphery of the nodules contained a few pigment-laden macrophages. This pigment was granular and golden brown in color, and presented the staining properties of hemosiderin. It was concluded that these features were those of eosinophilic granuloma of the lung.

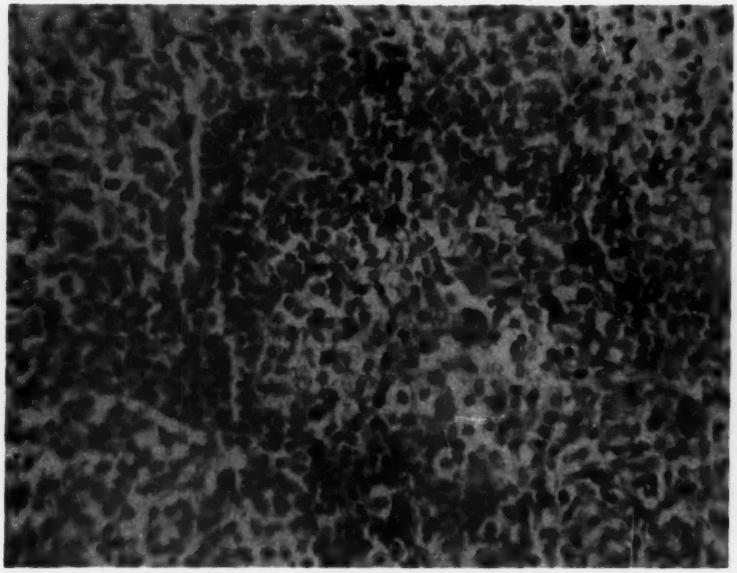

FIG. 5. Tissue from the femur presents oval collections of histiocytes and peripheral arrangement of eosinophils similar to pulmonary foci. H. and E. × 240.

Further Course in Hospital: After the pathologic diagnosis was established, roentgenographic survey examination of the skeleton was performed and revealed a discrete rarefaction in the superior third of the shaft of the right femur, characterized by lack of surrounding bony reaction and a cortical location. It lay on the lateral aspect of the femur and eroded the internal aspect of the cortex; there was firm and normal appearing cortex overlying the defect. Roentgen conclusion was that this represented a lesion of eosinophilic granuloma, particularly in view of the established diagnosis of the pulmonary lesions.

Because of the rarity of proved associated lesions of eosinophilic granuloma in the lung and in the skeleton, it was decided to explore the lesion of the femur for

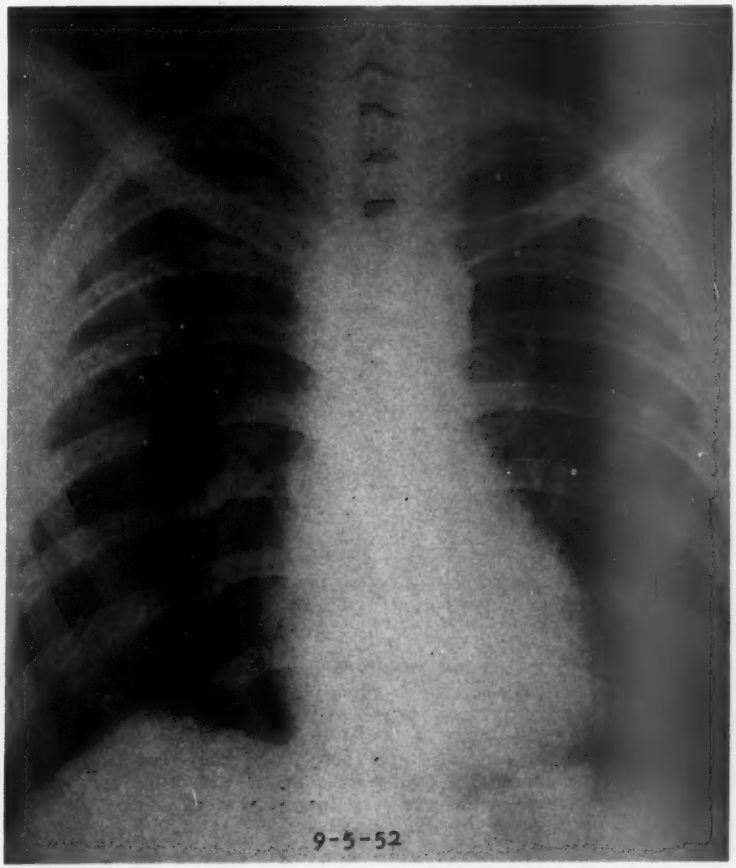

FIG. 6. September 5, 1952: Chest roentgenogram one month after completion of roentgen therapy to the lung fields. There is partial resolution of the pulmonary infiltrations and of some of the patchy coalescent areas in the upper lobes. A wire binder, a surgical residual, is noted about the anterior portions of the right fourth and fifth ribs.

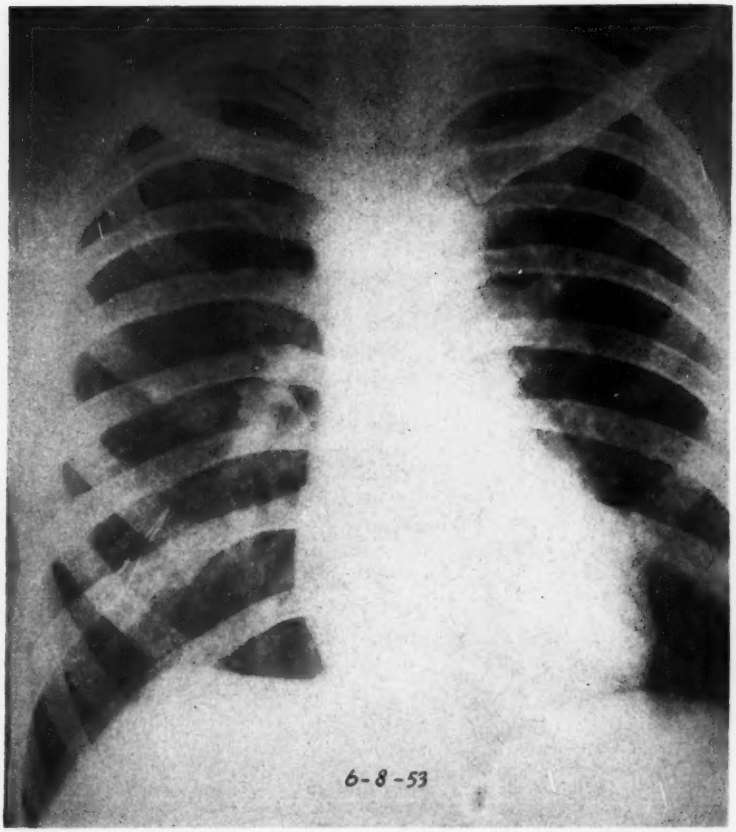

FIG. 7. June 8, 1953: Chest roentgenogram 10 months after roentgen therapy shows further resolution of the coalescent patches and interstitial infiltrations of the lungs. No other significant change in the thoracic structures is detected.

purposes of surgical curettage and biopsy. This procedure was carried out on July 15, 1952, by Dr. W. H. Ainsworth. A grayish yellow tumor mass was identified in the region located on the roentgenograms. After the overlying cortex was removed, curettage was performed. Gross examination of the curettements showed a yellowish gray, soft tissue which presented narrow septae of osseous tissue at one margin. This osseous tissue blended imperceptibly with the adjacent softer mass. The accompanying fragments of cortical bone varied from 1 to 3 mm. in thickness. Microscopic preparations from this tissue disclosed a lesion which had a histopathology similar to that of the pulmonary nodules (figure 5). There was minimal fibrosis and no areas of necrosis. Here again dense collections of eosinophils were noted.

The patient recovered from each of his operative procedures promptly and without complication. Because of the known radiosensitivity of eosinophilic granuloma, and because of the progressive nature of the patient's disability and roentgenographic

pulmonary findings, it was decided to treat the pulmonary lesions first by external roentgen therapy. After the bone biopsy was made a course of roentgen therapy was administered also to the lesion of the proximal third of the right femur. From July 8 to August 6, 1952, the lung fields were treated through two large anterior and two large posterior fields, each measuring 20 by 15 cm., supplemented by two smaller fields to the lowermost portion of the posterior thoracic wall on the right and left sides. A midthoracic tissue dosage of 1,200 r was achieved during this time.

The proximal third of the right femur was treated similarly through a field centered to the site of the granulomatous lesion, which had been curetted, and here a tissue dosage of 1,200 r was achieved in six days. The patient tolerated these courses of treatment without any difficulty.

FIG. 8. April 24, 1954: Chest roentgenogram, almost 21 months after roentgen therapy to the lungs, shows complete clearing of the coalescent inflammatory infiltrations originally present and resolution also of the pulmonary infiltrations. Minimal linear scarring is present in the right upper lobe.

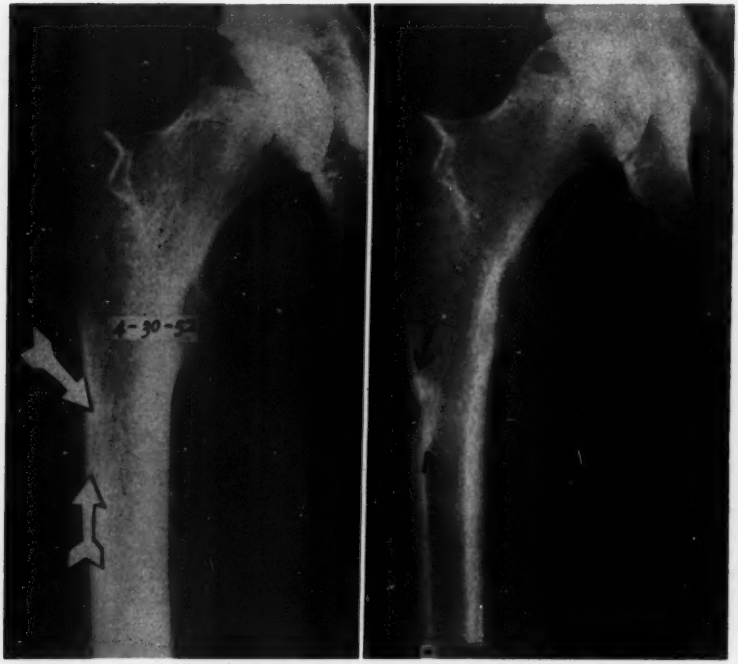

FIG. 9 FIG. 10

FIG. 9. April 30, 1952: Roentgenogram of the proximal third of the right femur reveals a discrete cystic rarefaction encroaching on the inner aspect of the cortex at the proximal end of the shaft (arrows). This appearance is compatible with a benign lesion such as eosinophilic granuloma.

FIG. 10. April 24, 1954: Roentgenogram of the proximal third of the right femur, almost 21 months after roentgen therapy, now reveals considerable sclerotic bone formation surrounding the granulomatous lesion, with elevation of the cortex internally and externally. This reparative process has been progressive to this time.

Chest Roentgenograms after Treatment: As early as September 5 (one month after completion of roentgen therapy), there was evidence of beginning resolution of the confluent areas of granulomatous pneumonitis in the upper lobes, with slightly better aeration and fewer alveolar blebs (figure 6). Examinations on June 8, 1953 (figure 7), and April 24, 1954 (figure 8), revealed progressive resolution. It can be seen from the illustration that by the latter date no confluent densities existed, but there was a minimal residual scarring of interstitial markings in the upper third of the right lung field. The cardiovascular outline, diaphragm and bony framework appeared normal at all times.

Roentgenograms of the Right Femur: The initial examination, on April 30, 1952 (figure 9), revealed the cystlike bone defect in the proximal third of the right femur, which was diagnosed as eosinophilic granuloma. A follow-up examination on April 24, 1954 (figure 10), shows healing and sclerosis of this lesion postoperatively and post-radiotherapeutically, with excessive periosteal calcification overlying it at the site of surgery.

Subsequent Course: After roentgen therapy the patient's general well being, vigor

and ability to work improved slowly at first but with somewhat greater acceleration after the third post-therapeutic month. Pulmonary function studies showed early improvement in that the resting minute ventilation fell and the maximal breathing capacity increased. Follow-up studies 12 months after the completion of therapy showed normal function. The patient noticed that he was able to walk further without the necessity of stopping to catch his breath until at the present time, 33 months after completion of roentgen therapy, his physical tolerance to exercise seems normal.

Discussion

This case is unusual in that histologic proof is available for the diagnosis of eosinophilic granulomatosis of the lungs and right femur, in each location. The diagnostic features of the case bear out the chest roentgenographic findings cited by previous observers, namely, the presence of a diffuse interstitial granulomatous disease accompanied by alveolar emphysematous blebs, and the absence of hilar or mediastinal lymphadenopathy. With these findings there is a progressive decrease in the individual's ability to exercise without dyspnea. The possibility of occupational or geographic factors in the etiology cannot be evaluated, inasmuch as no consistent pattern has appeared from this and previous case studies. The bone findings in our case were discovered by routine skeletal-roentgenographic survey and were not accompanied by localized symptoms.

Response to radiation therapy was gratifying and in keeping with the known radiosensitivity of this essentially benign lesion. Restoration of this individual to normal physical capacity and full working status was accomplished by a moderate tissue dosage to the femur and particularly to the lungs, with due regard to the possible hazard of late postradiation changes. Fortunately, tissue dosage can be limited to moderate levels in this disease, with satisfactory physical and roentgenographic improvement.

Lichtenstein [19] has suggested that Hand-Schüller-Christian disease, Letterer-Siwe disease and eosinophilic granuloma of bone be classified as "Histocytosis X." The findings in this case are morphologically similar to the lesions described by Farinacci et al.[16] and May et al.,[18] thereby confirming the systemic nature of the pathologic process as well as the close relationship of eosinophilic granuloma to Hand-Schüller-Christian and Letterer-Siwe disease. Due to the difference in the prognosis and therapy, these diseases should be differentiated by clinical and pathologic studies. This is particularly important from the prognostic standpoint for the more malignant form, Letterer-Siwe disease.

Summary

A case is reported of eosinophilic granuloma of the lungs and femur, both lesions being proved histologically. This 24 year old white male has remained symptom-free for 33 months following roentgen therapy of the chest and femur.

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THE ASSOCIATION OF THROMBOTIC THROMBOCYTOPENIC PURPURA AND DISSEMINATED LUPUS ERYTHEMATOSUS: REPORT OF A CASE*

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THE first description of a case of thrombotic thrombocytopenic purpura was given in 1925 by Moschcowitz,[1] who reported a case of acute febrile hemolytic anemia with petechiae and the development of neurologic signs shortly before death. Microscopic examination showed hyaline thrombi in terminal arterioles

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and capillaries. In 1936 Baehr et al.[2] reported four cases. They believed that the thrombi were composed of platelets. Since then more than 40 case reports have appeared in the literature. An excellent review of the literature has recently been presented by Barondess.[3] The syndrome has been clearly characterized by the clinical triad of hemolytic anemia, thrombocytopenic purpura and involvement of the central nervous system. The illness is associated with a febrile course and is often fulminating.

The cause of the disease is unknown. Several case reports have suggested a relationship to the so-called "collagen" diseases in general and to lupus erythematosus in particular. The following case is remarkable in that the patient presented a classic clinical and pathologic picture of disseminated lupus erythematosus in association with clinical findings suggestive of thrombotic thrombocytopenic purpura, confirmed on autopsy by the finding of widespread arteriolar and capillary platelet thrombi.

Case Report

A 33 year old housewife was admitted to the Jewish Hospital of Brooklyn on October 26, 1953. She had been in relatively good health until about eight years before admission, when she began to complain of pains in her wrists, elbows, knees and ankles. These joint pains were transitory in nature and were not associated with evidence of swelling, heat, redness or tenderness. The episodes of arthralgia were usually accompanied by low grade fever and slight anemia. She was told that she was suffering from rheumatoid arthritis. No specific therapy was instituted until about one year before admission, when she was started on gold injections and salicylates. In April, 1953, during an exacerbation of her joint symptoms, she was given phenylbutazone, with prompt relief. A complete blood count was performed every two weeks while she was maintained on phenylbutazone.

In August 1953 after several weeks of sunbathing, she complained of increased pain and swelling of her ankle joints. At about this time she noted the onset of headaches, fatigue, lassitude, weakness, anorexia and weight loss, and a temperature rise of 100° to 101° F. daily. About four weeks before admission black and blue patches began to appear spontaneously on all extremities, and on several occasions she passed tarry stools. During the week before admission the headaches became more severe and constant and were not relieved by codeine and aspirin.

Her childhood history was noncontributory. She was gravida II, para II. Past surgery included appendectomy in 1932 and hemorrhoidectomy and anal fistulectomy in 1946. Family history was not remarkable.

Physical examination on admission revealed a temperature of 100.6° F.; pulse, 104 per minute; respirations, 36 per minute; blood pressure, 112/65 mm. of Hg. The patient was a well developed, well nourished young white woman who appeared acutely ill. She was intermittently disoriented, poorly responsive, lethargic and somnolent. The exposed parts of the body were suntanned. Pallor of the mucous membranes and nail-beds was marked. There were many scattered ecchymotic and purpuric areas over the body. The sclerae had a yellow tint. There was an area of recent hemorrhage in the right fundus. Ears, nose and mouth were not remarkable except for pallor of the mucous membranes. The neck was supple. There were several enlarged lymph nodes in the posterior cervical chain, one large node in the left axilla, several small nodes in the right axilla and several nodes in both superficial inguinal chains. The lungs were clear to percussion and auscultation. The heart was not enlarged. The ventricular rate was 104 and the rhythm was regular. There were a soft apical systolic murmur and a loud harsh systolic murmur at the base, best heard over the pulmonic area. The second pulmonic sound was accentuated. First

heart tones were faint. No gallop rhythm or friction rub was heard. The abdomen was soft and the liver edge was palpable two fingerbreadths below the costal margin in the midclavicular line. The tip of the spleen was palpable below the left costal margin. Genital and rectal examinations were normal. Neurologic examination revealed no evident motor or sensory loss. Deep tendon reflexes were active and equal. Plantar responses were flexor bilaterally.

Laboratory studies were as follows:

The hemoglobin was 5.25 gm. %; hematocrit, 17%; red cell count, 1.5 million; corrected sedimentation rate, 20 mm. per hour; white cell count, 11,700; differential count showed juvenile forms, 12%; neutrophils, 58%; lymphocytes, 20%; monocytes, 6%; eosinophils, 4%; and the smear showed anisocytosis and poikilocytosis as well as polychromasia. There were 16 normoblasts per 100 white blood cells. There was a marked platelet deficiency on smear, and marked reticulocytosis was seen. Direct platelet count was 49,200. Urine was clear and amber and gave an alkaline reaction, with specific gravity of 1.008, one plus albumin, no sugar. The foam test for bile was negative, and the urine urobilinogen was positive in 1:50 dilution. The sediment of a centrifuged specimen contained occasional white blood cells and 3 to 8 red blood cells per high power field. The bleeding time was 13½ minutes and the clotting time was 3½ minutes. The tourniquet test was strongly positive. The direct and indirect Coombs' tests were negative. Stool test was negative for occult blood. The blood type was O, Rh positive. Mazzini test was negative. Blood chemical tests were as follows: blood sugar, 120 mg. %; urea nitrogen, 17 mg. %; icterus index, 30; albumin, 4.4 gm. %; globulin, 3.2 gm. %; alkaline phosphatase, 4 Bodansky units; cephalin flocculation, 0; thymol turbidity, 7.5 units; Bromsulphalein test showed 35% retained in blood after 45 minutes. Repeated blood cultures were sterile.

Aspirated sternal marrow disclosed a very marked shift to the left of the granulocyte series. The proportion of nucleated red cells was greatly increased. The megakaryocytes were mature and numerous, but no platelet formation was seen.

The patient lived for only six days after admission, and during this time she had a daily temperature rise to between 100° and 103° F. She was given two transfusions of whole blood and one transfusion of washed packed cells in the four days following admission, in addition to supportive therapy. Her condition remained about the same until two days prior to death, when she became severely disoriented, confused and semicomatose. An L.E. cell preparation by the two hour clot technic method done on this day showed abundant L.E. cells. ACTH therapy was started (20 mg. intramuscularly every six hours), but the course was progressively downward. She died suddenly on the seventh hospital day (the third day of corticotrophin therapy).

Autopsy was performed three hours after death. Permission for examination of the brain was withheld.

Autopsy Findings: The body was that of a well nourished and well developed white female. The sclerae were subicteric, and the abdomen was slightly distended and tympanitic. There were ecchymotic spots on the anterior and posterior surfaces of the lower and upper extremities.

Serous Cavities: Both pleural cavities were devoid of fluid content and contained slightly firm fibrinous adhesions of grayish white color. The pericardial cavity contained about 15 c.c. of a yellow fibrinous fluid and fibrinous adhesions similar to those previously described in the pleural cavities. The peritoneal cavity was free of abnormal or excessive fluid, and there were numerous slightly firm adhesions surrounding the spleen.

Heart: The heart weighed 350 gm. The external surface revealed scattered, diffuse, irregularly shaped subepicardial areas of hemorrhage. The right atrium

was slightly dilated and filled with clots of blood. The right ventricular wall measured 0.7 cm. in thickness. The left ventricular wall measured 2 cm. in thickness. There were diffuse, irregular hemorrhagic areas in the subendocardial surface. On section the myocardium showed petechial hemorrhagic areas at the cut surfaces of all the walls. The coronary arteries were patent and clear. The aorta showed no remarkable features.

Lungs: The right lung weighed 550 gm. The external surface was dull, purplish gray in color and anthracotic. Scattered throughout all lobes were subpleural petechial hemorrhagic areas. On section, the cut surface was purplish red, moderately congested and edematous. The pulmonary vessels and bronchi were patent, and the latter were filled with hemorrhagic material. The left lung weighed 350 gm. and showed features similar to those described in the right lung.

Stomach: The stomach showed the presence of petechial hemorrhagic areas scattered in the mucosal surface.

Liver: The liver weighed 2,100 gm. The external surface was brownish red, smooth and glistening. On section the cut surfaces showed irregularly distributed petechial hemorrhagic areas like those previously described in the other organs.

Spleen: The spleen weighed 350 gm. The external surface was purplish red and dull. It was moderately firm in consistency. The cut surface was deep purplish red, and markedly congested. The Malpighian corpuscles were prominent.

Kidney: The right and left kidneys weighed 190 gm. The external surface was reddish tan, smooth and glistening. Removal of the renal capsule left a smooth and glistening surface with a moderate number of petechial hemorrhagic areas scattered throughout the cortex. On section the cut surface showed a well demarcated cortex and medulla with the usual anatomic proportion. The medulla was red in color. The calyces, pelvis and ureters were patent throughout and were not grossly remarkable.

Microscopic Description: Thyroid: Some of the small arterioles showed portions of the wall (especially the intima) replaced by a deposit of homogeneous eosinophilic material (fibrinoid degeneration). The lumina of many of the arterioles as well as of the capillaries were completely or partially occluded by a finely granular eosinophilic substance which in places appeared encompassed by a single row of endothelial cells.

Heart: The preparations from the heart revealed the epicardium to be moderately thickened and covered for the most part by a pinkish fibrinous material infiltrated with plasma cells, lymphocytes, some leukocytes and large mononuclear cells with abundant eosinophilic cytoplasm. In some places the areolar portion of the epicardium was replaced by loose fibrous tissue with numerous capillaries engorged with blood and showing active fibroblastic proliferation and infiltration with plasma cells, lymphocytes and leukocytes. Some of the capillaries within this area were partially occluded by a homogeneous and somewhat granular eosinophilic material. In some portions the myocardial bundles were fragmented and there were scattered, irregularly shaped hemorrhagic areas. Some of the arterioles showed portions of the wall with moderate fibrinoid degeneration, and many of them as well as the capillaries revealed the lumina partially or completely filled with eosinophilic homogeneous and somewhat finely granular material (figure 1). The endocardium was for the most part not remarkable. In one preparation the endocardium appeared fragmented and replaced by a finely fibrillar pink staining tissue infiltrated with enlarged mononuclear cells with eosinophilic cytoplasm. A few of the small coronary branches showed fibrinoid degeneration of the wall.

Lungs: The superficial portion of the pleura was composed for the most part of loose connective tissue with formation of new capillaries and infiltrated with active fibroblasts, extravasated blood cells and large mononuclear cells with eosinophilic cytoplasm. The deeper portion of the pleura was represented by irregularly thickened, intensely eosinophilic and highly refractile and swollen fibers whose massiveness was

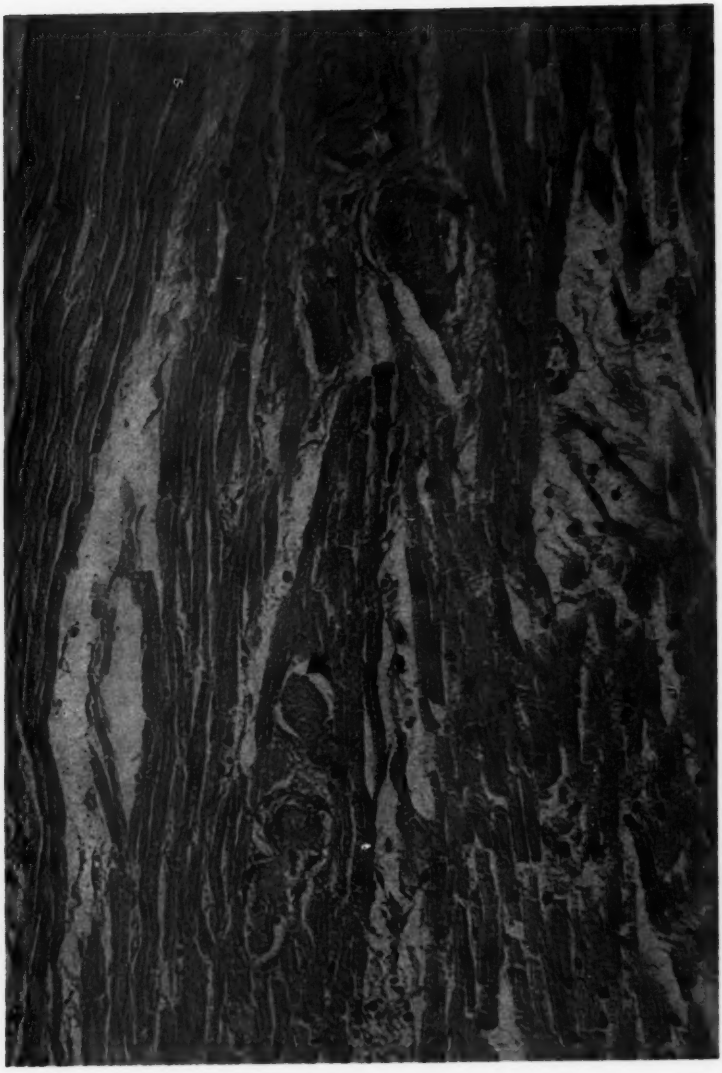

FIG. 1. Section of heart showing thrombi within the lumina of the capillaries and arterioles and the fibrinoid degeneration of a portion of the wall of the latter. × 300.

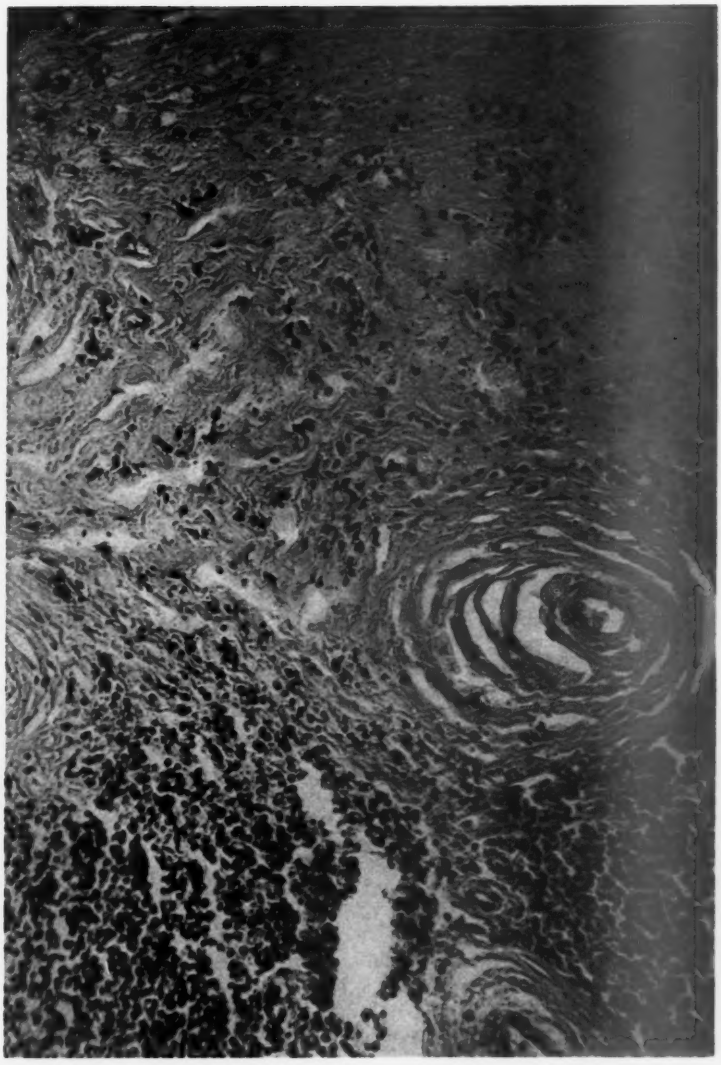

FIG. 2. Section of spleen showing the "onion peel" lesion characteristic of disseminated lupus. × 500.

of a portion of the wall of the latter. × 300.

augmented by the accretion of adherent clumps of ground substance. Some of the small and middle sized pulmonary arteries showed mural fibrinoid changes, especially of the adventitia, with proliferation of the adventitial cells. Some of the capillaries also contained thrombi. A fair number of megakaryocytes were seen in the small vessels throughout all the preparations.

Liver: The preparations from the liver showed the capsule to be moderately thickened and represented for the most part by wavy, irregularly thickened, intensely eosinophilic fibers. Irregularly distributed within many of the lobules were necrotic hemorrhagic areas. Some of the portal and hepatic veins showed fibrinoid degeneration subendothelially, and many of them appeared partially or completely occluded by thrombi. Some of the hepatic arterioles were slightly narrowed and showed also moderate fibrinoid degeneration of the intima.

Pancreas: Throughout the preparation many of the small arterioles and capillaries were partially or completely occluded by thrombi.

Spleen: The preparation from the spleen showed the capsule to be moderately thickened and composed of hyalinized fibrous connective tissue. The external surface was covered by a pinkish fibroblastic tissue infiltrated with plasma cells, lymphocytes, some leukocytes and enlarged mononuclear cells with eosinophilic cytoplasm. Many of the central and penicillate arteries showed concentric lamination of rings of stout collagenous fibers with a few intercalated fibroblasts assuming an "onion peel arrangement" (figure 2). Some of the arterioles were partially occluded by thrombi (figure 3).

Stomach: The capillaries within the submucosa were dilated, and many of them were partially obliterated by eosinophilic thrombi.

Adrenals: Many of the capillaries noted in the areolar tissue surrounding the capsule were filled with thrombi. Scattered throughout some of the preparations were irregular necrotic hemorrhagic areas within the cortex. Many of the capillaries were also partially or completely occluded by thrombi.

Kidneys: The preparations from the kidneys revealed the capsule to be of the usual thickness and composed of fibrous connective tissue. The intraglomerular capillary loops showed focal acidophilic, homogeneous and nongranular thickening of one or more segments of the wall. Such loops were somewhat rigid and the thickening was found between the endothelium and visceral epithelium (basement membrane), giving the so-called "wire-loop" appearance (figure 4). In some of the glomeruli the loops appeared completely necrotic and were represented by a mass of acidophilic and basophilic debris containing nuclear fragments adherent to the capsule. Elsewhere there were eosinophilic thrombi within the lumina of the capillary loops. The capillaries were engorged with red blood cells, and many of them as well as small arterioles were partially or completely obliterated by thrombi. Scattered irregularly throughout the preparation of the cortex were numerous hemorrhagic areas.

Bone Marrow: Scattered throughout the preparation were many endothelial spaces, partially or completely obliterated by deeply eosinophilic thrombi.

Anatomic Diagnosis: (1) Disseminated arteriolar and capillary platelet thrombosis. (2) Generalized petechial hemorrhage and subcutaneous ecchymosis. (3) Disseminated lupus erythematosus involving: (a) Kidneys, spleen, heart, liver, lungs and thyroid gland; (b) Serous cavities (pleuritis, fibrous pleural adhesions and perisplenitis). (4) Lungs with marked edema and congestion. (5) Focal necrosis of liver and adrenal glands.

Discussion

This patient presented a history of intermittent arthralgia for eight years with no other symptomatology of disseminated lupus erythematosus until the rapid downhill course was precipitated by exposure to sunlight. This phe-

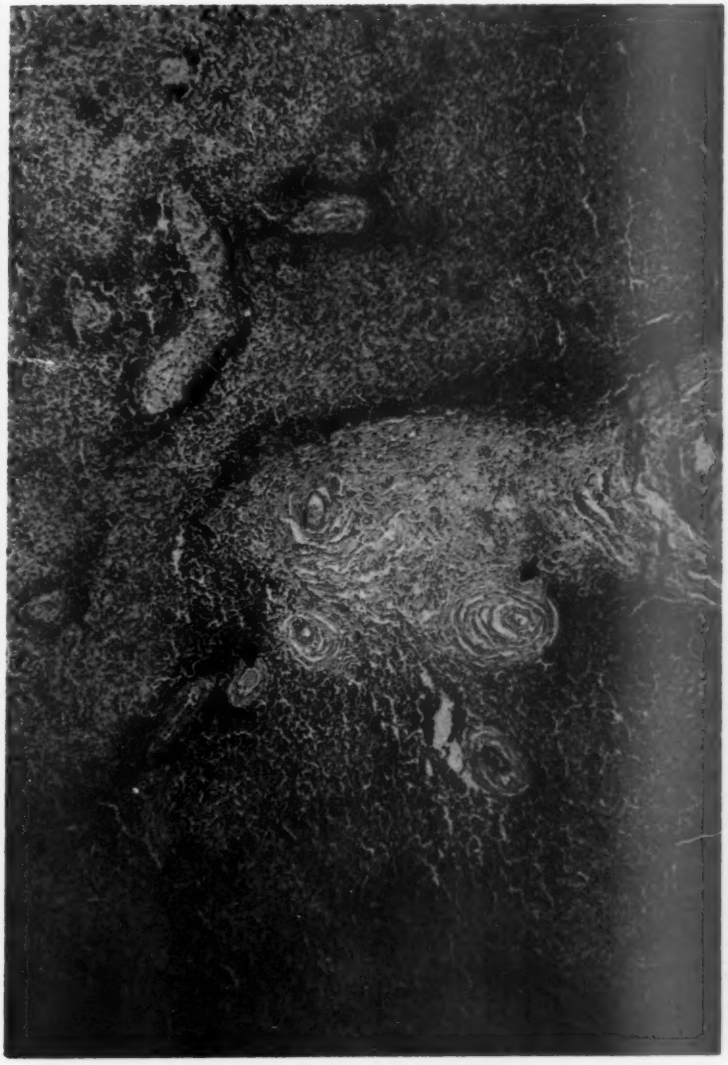

FIG. 3. Section of spleen showing the "onion peel" lesion in the arteriole (lower portion) and thrombi within the arteriolar lumen (upper portion). × 300.

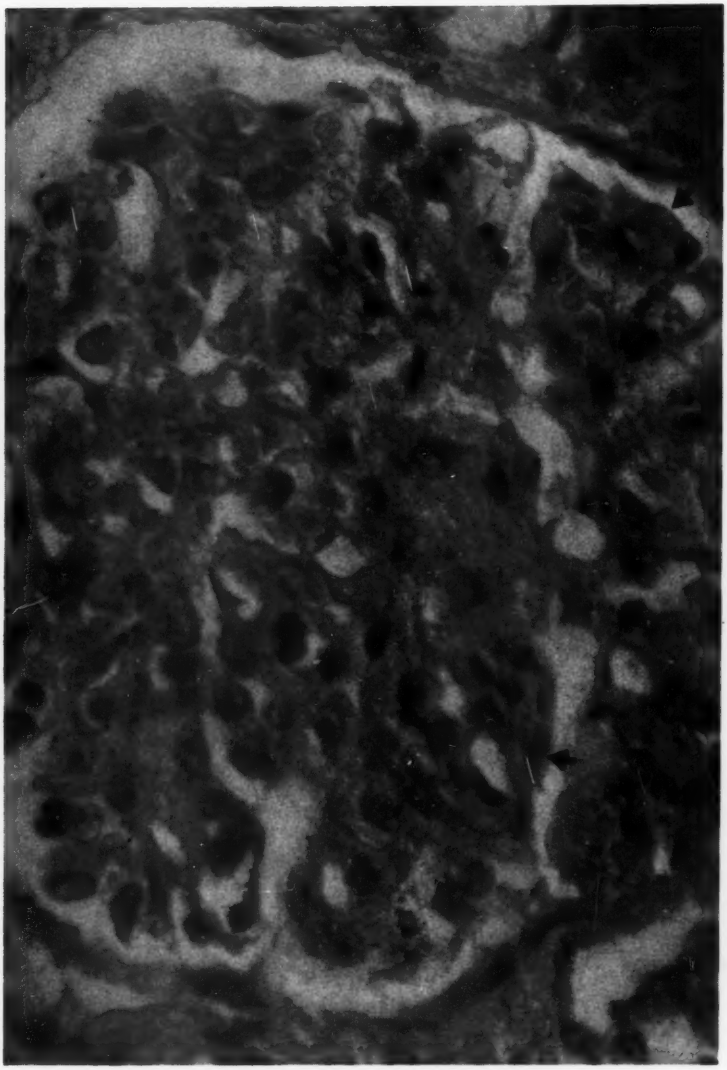

FIG. 4. Section of kidney showing a glomerulus with the "wire-loop" appearance of the capillary loops. × 500.

nomenon has not been satisfactorily explained, and despite the occasional demonstration of increased porphyrin excretion,[4] a definite abnormality in porphyrin metabolism has not been proved.

The fever, the weakness, the appearance of purpura, the lymphadenopathy, the hepatosplenomegaly, the abnormal urinary findings, the thrombocytopenia and the progressive anemia presented the characteristics of disseminated lupus erythematosus. The clinical impression was confirmed by the finding of abundant L.E. cells in the peripheral blood. Michael et al.[5] recently reviewed in detail the results of blood examinations of a large group of patients with disseminated lupus erythematosus. They found thrombocytopenia (150,000 or less) in 43 out of a total of 83 patients with proved disseminated lupus erythematosus. They presented two cases in which a severe thrombocytopenia was the initial manifestation of this disease.

Hemolytic anemia may occur in patients with disseminated lupus.[5, 6] Dubois reported three cases with the presenting syndrome of acquired hemolytic anemia, followed subsequently by the classic picture. The Coombs' test was positive in all three cases. In one of Michael's [5] three cases with acquired hemolytic anemia the Coombs' test was positive. Thus the over-all clinical picture in our case served to justify a presumptive diagnosis of disseminated lupus erythematosus, and this was corroborated by the finding of the "L.E." cell [7] in the peripheral blood.

The clinical and laboratory features were also consistent with a diagnosis of thrombotic thrombocytopenic purpura. Evidences of hemolytic anemia (icterus, anemia, nucleated red blood cells in peripheral blood) and terminal cerebral manifestations were all in accord with such a diagnosis. It is of interest that the Coombs' test was negative in both cases of thrombotic thrombocytopenic purpura reported by Cooper et al.,[8] as it was in our case. In a case reported by Green and Green [9] no antibodies were demonstrable with the serum, albumin and Coombs' tests. Detailed hematologic and immunologic investigations performed on a patient with thrombotic thrombocytopenic purpura by Singer, Motulsky and Shanberge [10] revealed a hemolytic process unaccompanied by evidence of auto-immunization. This suggests that the hemolysis is not mediated through a globulin antibody.

It is probable that our patient had had disseminated lupus erythematosus in a latent form for many years, with an acute activation of the disease process following exposure to sunlight. The rapid downhill course could then be attributed to fulminating thrombotic thrombocytopenic purpura.

Antemortem diagnosis of the latter disease varies with the index of suspicion. In addition to the clinical and laboratory findings, Cooper et al.[8] presented another method by which the presumptive diagnosis may be confirmed. He reported two cases of thrombotic thrombocytopenic purpura in which the clinical diagnosis was verified before death by demonstration of typical vascular lesions in microscopic sections of aspirated bits of sternal bone marrow.

The true nature of thrombotic thrombocytopenic purpura remains unknown. For many years the thrombocytopenia was attributed to the fact that the platelets were used up in the formation of multiple "platelet" thrombi. This has never been directly demonstrated. Meacham et al.[11] reported a case that showed no platelet formation from megakaryocytes in the marrow, suggesting to the authors that the thrombocytopenia may not be due simply to massive deposition of plate-

lets in small vessels. In both cases reported by Cooper et al.,[9] although megakaryocytes appeared adequate in number in the stained films of blood from sternal marrow there was little evidence of normal platelet production. The authors were inclined to believe that thrombocytopenia is chiefly the result of underproduction rather than of overutilization. Similarly, in our case, although sternal marrow revealed numerous megakaryocytes, platelet formation was absent.

Altschule[12] in 1942 first suggested that the occlusions might be secondary to a primary vascular change. Gore[13] recently demonstrated a "prethrombotic" vascular lesion, subendothelial in location, with secondary accumulation of platelets on a tiny overlying endothelial defect. Orbison[14] serially examined the arterial walls and found focal amorphous eosinophilic lesions which replaced the normal components of the wall and in some instances were continuous with the intraluminal masses. These findings, he believed, supported the concept of a primary arterial lesion. Thrombi containing platelets and fibrin may then develop at such sites of endothelial involvement.

The question of a possible relationship of thrombotic thrombocytopenic purpura to the "collagen" diseases has come to the foreground in recent years. In 1939 Gitlow and Goldmark[15] compared the findings of a case of disseminated lupus erythematosus with another case which showed "hyaline masses" and a suggestion of the so-called "wire-loop" appearance in the glomeruli. No thrombotic lesions were seen in the vessels of the other viscera, however.

The relationship of disseminated lupus erythematosus and thrombotic thrombocytopenic purpura was denied by several authors.[2, 12, 13, 16, 17] Pagel,[18] however, reported two cases of subacute bacterial endocarditis in which small fibrin thrombi and endothelial cell thrombi in the venous sinuses of the skin were thought to be the cause of acronecrosis. Similar platelet thrombi were observed by him in the smaller branches of the pulmonary artery in a third case of subacute bacterial endocarditis. In two of his cases there were definite fibrinoid changes in the renal glomeruli. The "wire-loop" pattern of lupus erythematosus was manifested in one case. Thus he showed the association of platelet thrombosis and the changes characteristic of a "collagen" disease.

Beigelman[19] has considered the association of the two conditions favorably. He reported two cases in which, in addition to the lesions of thrombotic thrombocytopenic purpura, features thought to suggest disseminated lupus erythematosus were found. The first case revealed many platelet thrombi in the myocardium, in addition to focal hyaline necrosis in the glomerular capillaries and splenic perifollicular rings of the lupus type. In the second case antemortem diagnosis of thrombotic thrombocytopenic purpura was confirmed by the finding of platelet thrombi in a skin specimen. Autopsy revealed advanced glomerular lesions as well as verrucous endocarditis of the aortic valve. The author has suggested that differing syndromes of "collagen" disease would result depending on the part of the vessel which acted as the shock organ. A reaction in the intima would result in platelet thrombosis; a reaction within the vessel wall, in periarteritis nodosa; and a hyperergic reaction in the perivascular mesenchyme would be represented by lupus erythematosus.

Symmers and Gillett[20] reported a case of polyarteritis nodosa in which widely disseminated lesions of platelet thrombi were also present, although there were no detectable manifestations of their presence during life. In another case

of thrombotic thrombocytopenic purpura presented by Symmers and Barrowcliff,[21] "wire-loop" lesions indistinguishable from those of disseminated lupus erythematosus were found in the glomeruli.

The finding at autopsy of nonbacterial verrucous endocarditis similar to the type seen in disseminated lupus has been reported in several cases of thrombotic thrombocytopenic purpura.[2, 3, 11, 22, 23] In one case reported by Barondess[3] there were lesions in the spleen which were quite characteristic of disseminated lupus erythematosus, although the patient presented nothing clinically suggestive of the latter disease.

A possible example of a familial relationship has been reported by Bernheim,[24] who presented a patient with thrombotic thrombocytopenic purpura whose brother died with periarteritis nodosa. Singer et al.[10] mentioned the development of thrombotic thrombocytopenic purpura in a sibling of a woman with disseminated lupus erythematosus.

In the case presented in this report, many platelet thrombi were noted at autopsy in all the organ systems of the body. Although nonbacterial verrucous endocarditis was absent, the classic findings of disseminated lupus erythematosus were present in the kidney and spleen and in the walls of the serous cavities of the body. It would appear that the association of the two conditions in the same patient is more than coincidental. This case, then, tends to support the newly propounded theory that thrombotic thrombocytopenic purpura should be placed in the category of the "collagen" diseases. Further clinical and pathologic research and/or the elucidation of an etiologic factor may throw further light on the probability of such a relationship.

With regard to therapy, a word of caution is in order based on our findings. As soon as the diagnosis of disseminated lupus was confirmed a course of adrenocorticotrophin was instituted. Aside from the fact that it was probably instituted too late in the disease, the failure of ACTH to influence the clinical course can be attributed to the findings of hemorrhage, thromboses and focal necrosis in the cortex of the adrenal gland. Hence it would appear advisable to use cortisone rather than ACTH in fulminating purpuras with suspected visceral involvement.

Summary

A case of thrombotic thrombocytopenic purpura in association with disseminated lupus erythematosus is presented. The diagnosis of disseminated lupus erythematosus was confirmed ante mortem on the basis of a positive "L.E. cell" preparation. Autopsy also showed the presence of platelet thrombi. In this case the triad of thrombocytopenic purpura, hemolytic anemia and cerebral manifestations was encountered. Because of the association of the two disease processes, it is suggested that thrombotic thrombocytopenic purpura may belong in the category of "collagen" diseases.

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GAUCHER'S DISEASE WITH ASCITES: A CASE REPORT WITH AUTOPSY FINDINGS *

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SINCE the original description of this disease in 1882, reports of approximately 280 cases have appeared in the literature. The condition was originally considered to be a primary splenic epithelioma,[1] and it was Gaucher who first described the cells in the spleen characteristic of this disease. The involvement of the liver by these cells was observed by Bovaird [2] in 1900. The classic features of Gaucher's disease—hepatosplenomegaly, brownish pigmentation of the skin, pingueculae, bone marrow infiltration with resulting anemia, leukopenia, thrombocytopenia, osseous changes, and central nervous system manifestations in infants —are well known. Despite the frequent involvement of the liver, aberrations in liver function tests are uncommon.[3, 4] It is recognized by most writers that ascites is rare.[3, 5, 6] The following case of Gaucher's disease is presented because ascites and derangement of liver function were prominent features. The pathology and possible pathophysiology will be discussed.

CASE REPORT

A 61 year old white male was admitted to the Jewish Hospital of Brooklyn on November 23, 1953, complaining of dyspnea and swelling of the abdomen, scrotum, penis and lower extremities of three weeks' duration. At the age of 16 he was examined because the diagnosis of Gaucher's disease had been made on his brother, and at that time he was found to have an enlarged spleen. Over the ensuing years the patient tolerated his large spleen well and was able to carry on an active dental practice. He was under the observation of a hematologist for more than 15 years, during which time the patient had a leukopenia, thrombocytopenia and mild anemia, which required no transfusions or hematinics. In the past there had been no gross bleeding tendency except for occasional slight blood loss from the gums and hemorrhoids. For the last 10 years the patient had been aware of mild pitting edema of the lower extremities extending up to his knees, as well as a brownish pigmentation of the skin over these areas. Until three weeks prior to admission, the only other symptom of which he was aware was slowly progressive enlargement of his spleen for the past 45 years. Three weeks prior to admission the patient noted rapid and progressive abdominal distention associated with scrotal swelling and markedly increasing edema of both lower extremities extending to the thighs. For the first time he became short of breath on exertion and unable to carry on his usual activities. He was unable to lie flat. There was no history of anorexia, dysphagia, food intolerance, excessive alcohol intake, inadequate food intake, jaundice, hepatitis or abdominal pain. He had not received any blood transfusions. His past medical history and review of systems were noncontributory. Physical examination revealed: blood pressure, 126/80 mm. of Hg; pulse, 88; respirations, 28; temperature, 98° F. The patient was a poorly nourished, asthenic white male with a greatly enlarged abdomen. He was slightly orthopneic. The skin had a buckwheat pallor. There was no icterus or cyanosis. Examination of the head and neck revealed no significant abnormalities. The heart and lungs were normal. There was no adenopathy. The abdomen was markedly protuberant and the umbilicus everted. Some superficial

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venous distention was noted. A fluid wave was easily elicited. The spleen occupied the entire left side of the abdomen and extended into the pelvis and right lower quadrant. It was firm, smooth, nontender and easily movable. The liver edge was palpable two fingerbreadths below the right costal margin; it was firm and nontender. The character of the liver surface could not be determined because of the massive ascites. No other abdominal masses were palpable. There was marked edema of the scrotum and the skin proximal to the glans penis. The testes could not be evaluated because of this edema. Rectal examination revealed thrombosed internal hemorrhoids. There was no clubbing of the fingers or toes. There was a 4 plus pitting edema of the lower extremities extending into the thighs and the sacral area. The legs showed brownish pigmentation characteristic of Gaucher's disease. In addition, there were several areas of stasis dermatitis. Neurologic examination showed no abnormalities.

Laboratory and X-ray Findings: The hemogram revealed 11.5 gm. of hemoglobin; 4.2 million red blood cells; 2,350 white blood cells, with a differential of 70% polys, 2% bands, 25% lymphocytes and 3% eosinophils. The hematocrit was 43%. Sedimentation rate was 8 mm./hr. (Westergren). Bleeding and clotting times were normal. The platelet count was 10,000 per cubic millimeter. The Rumpel-Leede test was markedly positive and clot retraction was impaired. Coombs' test was negative. The urine showed a trace of albumin, was slightly positive for bile and contained urobilinogen in 1:60 dilution. Phenolsulfonphthalein excretion and urine concentration and dilution were normal. There was no blood in the stool. The Mazzini test was negative.

The abnormal blood chemistries were: urea nitrogen, 25 mg. %; uric acid, 6.2 mg. %; serum bilirubin, 1.3 mg. %, with 75% direct; icterus index, 12.7; cephalin flocculation, 1 to 2 plus; total cholesterol, 80 mg. %, 28% free; total protein, 4.9 to 5.6 gm. %; albumin-globulin ratio, 0.8; bromsulphalein retention, 38% in 45 minutes; prothrombin time, 15 to 21 seconds. The glucose tolerance curve was: fasting, 95 mg. %; one-half hour, 129 mg. %; one hour, 173 mg. %; two hours, 219 mg. %; three hours, 145 mg. %. This is consistent with hepatic damage. The fasting blood sugar, alkaline phosphatase, electrolytes, thymol turbidity and serum lipids were normal.

The bone marrow showed active erythrogenesis, a shift to the left of the granulocytic series and adequate megakaryocytes. Many Gaucher's cells were noted (figure 1). Needle aspiration of the spleen revealed many Gaucher's cells, with no evidence of extramedullary hematopoiesis (figure 2). X-rays of the chest and upper gastrointestinal tract were normal. The femora showed thinning of the cortices and intramedullary sclerosis of the distal portions. There were sclerotic changes in the left hemipelvis. Both of these changes were consistent with Gaucher's disease. The electrocardiogram showed no abnormalities.

Clinical Course: In the hospital the patient failed to respond to intensive diuretic therapy, which included mercuhydrin and aminophylline. On December 2, 11 days after his admission, a paracentesis was performed and 5,200 c.c. of slightly pink fluid were obtained which showed a specific gravity of 1.010 and total protein of 0.8 gm. %. Culture of the fluid and cytology (cell block) were negative. On continued diuretic therapy there was only minimal reaccumulation of the ascitic fluid. Splenectomy was advised. The patient refused surgery and was discharged on December 23. Other therapy included two transfusions, crude liver extract, vitamin K, therapeutic vitamin capsules and Methiscol.

The patient was re-admitted on December 27, 1953. Two days prior to this admission he had experienced sudden onset of pain in the right groin and thigh. Swelling and redness were soon noted in this area. The pain was progressive, and redness and swelling appeared in the left thigh a few hours later. On the day of

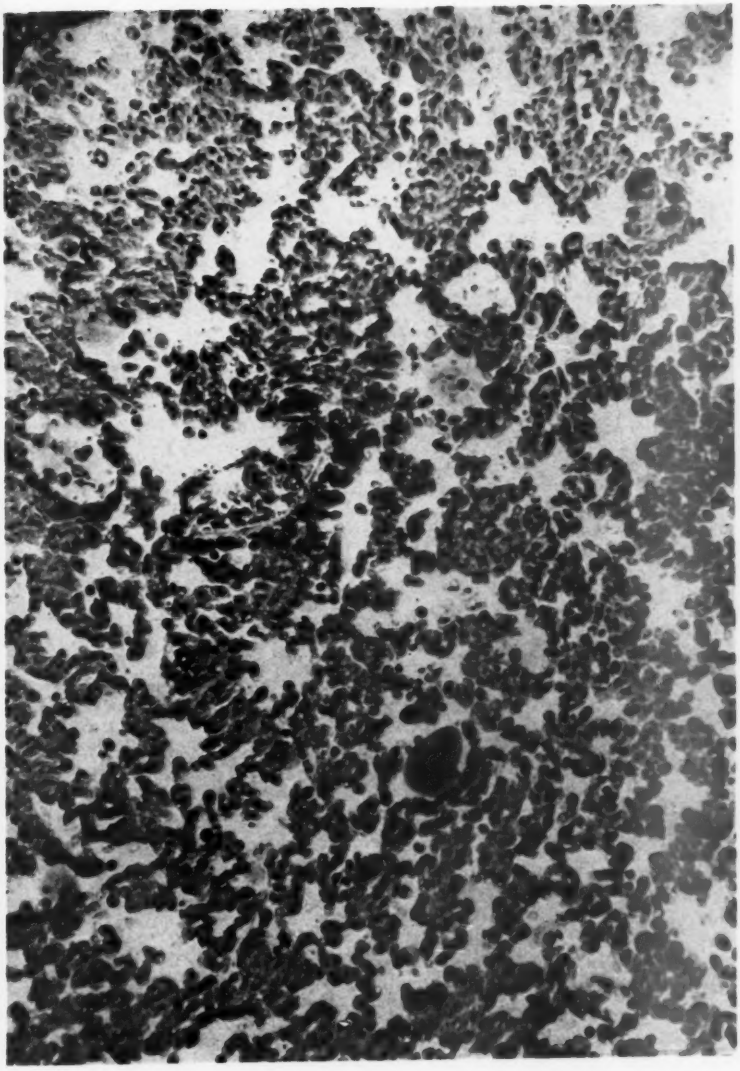

FIG. 1. Bone marrow aspiration, × 300; note megakaryocyte and Gaucher's cells.

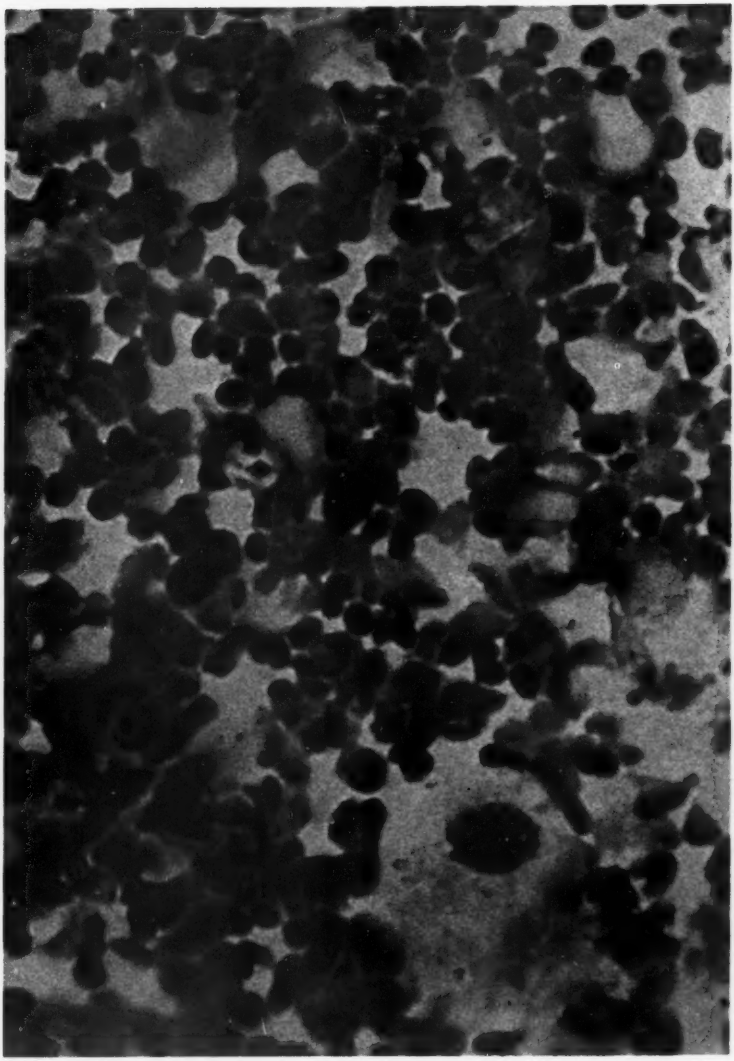

FIG. 2. Spleen aspiration, × 500; note Gaucher's cell.

admission the patient became disoriented, but responded to commands and painful stimuli. He appeared toxic. The skin was hot and dry, and dehydration was apparent. The blood pressure was 90/60 mm. of Hg; pulse, 180; respirations, 40 and shallow; temperature, 103° F. The electrocardiogram revealed auricular tachycardia. There were areas of ecchymosis suprapubically and in both flanks. The thighs were swollen, warm, edematous and ecchymotic. The patient's condition deteriorated rapidly. Chemistries at this time were as follows: urea nitrogen, 62 mg. %; CO_2, 11.7 mEq.; chloride, 90.4 mEq.; potassium, 6.5 mEq.; fasting blood sugar, 53 mg. %. The urine showed 2 plus albumin and many red and white cells. A blood culture (which was reported post mortem) revealed 500 colonies of *E. coli* per cubic millimeter in all media. Despite therapy with intravenous antibiotics, pressor substances and adrenal cortical extract, the patient died six hours after admission.

Postmortem examination revealed the following: The skin was lemon-yellow and there was brownish pigmentation over the legs, buttocks and thighs. Scattered ecchymotic areas were present over both lower extremities and in the pubic area. Each pleural cavity contained 400 c.c. of straw-colored fluid. The main gross findings were in the abdominal cavity, which contained 6,000 c.c. of pinkish yellow fluid. The spleen weighed 5,550 gm. The cut surface was hemorrhagic; no Malpighian corpuscles or trabeculae were seen. There were areas of old and recent infarction, some calcified (figure 3). The liver weighed 2,150 gm. Its surface was firm and nodular, with depressed fibrous strands separating the nodules. The portal and systemic abdominal vessels were patent.

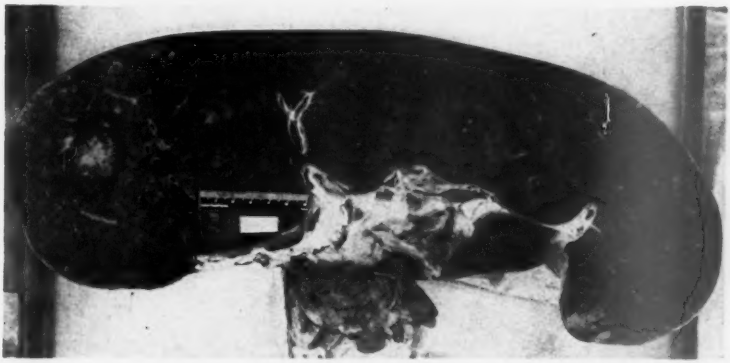

FIG. 3. Gross appearance of cut section of spleen; areas of old and recent infarction are present, some of which are calcified.

On microscopic examination the liver capsule was thickened. The lobular pattern was completely destroyed, and no central veins or portal vessels were clearly identified. The liver cells were grouped into irregular nodules of regenerative hyperplasia of varying sizes. These cells were swollen and laden with brown pigment. The liver cords were irregular and widely separated by distended sinusoids. The sinusoids and perinodular collagenous and fibrous tissues were packed with lipoid-laden cells (figure 4). These cells were large and oval with sharply defined cell borders. The nuclei were round or oval and eccentrically placed, and contained distinct nucleoli. The cytoplasm was pale pink and foamy, with pink longitudinal striae. Some of the cells were multinucleated. There were collapsed bile ducts, engorged capillaries and several small foci of extramedullary hematopoietic cells. The

FIG. 4. Liver, × 300; note almost complete replacement of liver tissue by Gaucher's cells.

FIG. 5. Posterior lobe of pituitary, × 1000; a large Gaucher's cell is in the center of the field.

capsule of the spleen consisted of thick, wavy, hyalinized fibrous connective tissue. The trabeculae and remnants of Malpighian corpuscles were occasionally seen. The cyto-architecture was completely destroyed and was replaced by intercommunicating sheets of closely packed, lipoid-laden cells of the type noted in the liver. The sheets of cells were separated by thick bands of fibrous tissue. Scattered throughout the fibrous tissue were areas of hemorrhage, brown pigmentation, calcification, and foci of extramedullary hematopoietic cells. Lipoid laden "Gaucher's cells" were present in the posterior lobe of the pituitary gland (figure 5) and in the bone marrow. The heart showed coronary artery sclerosis, myocardial fibrosis and toxic myocarditis. The lungs revealed passive congestion, focal atelectasis and emphysema. An accidental finding was an anterior mediastinal tumor weighing 100 gm., which on microscopic section proved to be thymic carcinoma.

Discussion

This patient exhibited most of the common findings of Gaucher's disease, including hepatosplenomegaly, pigmentation of the skin, bone changes, anemia, leukopenia and thrombocytopenia. Typical Gaucher's cells were found in smears of material obtained by aspiration from the spleen and bone marrow. It is probable that hypersplenism [7] contributed to the hematologic picture, as evidenced by splenomegaly, panhematocytopenia and an active marrow.

In reviewing the literature we have been unable to find any case in which ascites was a feature of Gaucher's disease. One case with clinical ascites was proved to have tuberculous peritonitis on postmortem examination.[8] The question of some associated pathology, i.e., intra-abdominal malignancy, cirrhosis, tuberculous peritonitis, portal vein thrombosis, was considered ante mortem because of the knowledge that ascites in Gaucher's disease is rare. However, no accompanying disease process was found to account for the marked ascites. The extensive parenchymal infiltration of the liver by Gaucher's cells with destruction of liver architecture undoubtedly explains the alterations in liver function in this case. With the obliteration of central veins and sinusoids, and the compression of the portal triads by Gaucher's cells and connective tissue, it seems reasonable to assume that an element of portal hypertension was present. The combination of portal hypertension, hypoalbuminemia and other known factors due to aberration of liver function may be invoked to explain the ascites in this case.

Abnormalities in liver function tests in Gaucher's disease were considered uncommon until recent years.[3, 9] The most common disturbances are elevation of the serum bilirubin and delayed excretion of Bromsulphalein. In this case not only were the serum bilirubin and Bromsulphalein excretion elevated, but also the total cholesterol and the serum albumin were greatly reduced, the cephalin flocculation test was positive, and the prothrombin time and the glucose tolerance curve were elevated. These are all evidence of impairment of liver function more severe than has heretofore been reported in cases of Gaucher's disease. The presence of ascites and moderate liver damage in a patient with proved Gaucher's disease does not necessarily imply the coexistence of another disease. These findings may be attributable solely to extensive involvement of the liver with Gaucher's cells and the attendant disruption of liver function. However, because of the rarity of this situation, a search for an accompanying disease should be conducted.

Gaucher's cells in the posterior lobe of the pituitary gland were first reported

by Telium,[10] who hypothesized that the microglia of the posterior lobe were related to the reticuloendothelial system. Small numbers of Gaucher's cells were found in the posterior lobe of the pituitary gland in this patient.

Summary

A case of long-standing Gaucher's disease is presented. In addition to the usual characteristics of the disease, this patient had prominent ascites and impaired liver function tests. An explanation for this is offered. An incidental finding was the presence of Gaucher's cells in the posterior lobe of the pituitary gland.

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EDITORIAL

RABIES IN BATS

THE recovery of rabies virus from bats living under natural conditions in the United States indicates the need of reassessing the importance of these animals as a reservoir and carrier of the infection. The earliest pertinent observations concern an epizootic in cattle and other herbivora observed in 1906 to 1908 in Santa Catarina, near the sea coast in southern Brazil. The affected animals invariably died after an illness of about a week, characterized by a progressive ascending paralysis, associated with salivation, difficulty in swallowing, emaciation and finally respiratory failure. At first this was erroneously diagnosed as "mal de caderas de bovinos." The inhabitants occasionally noticed as an unusual phenomenon that bats were flying about during the day fighting with each other and biting the cattle. As animals so bitten commonly soon sickened and died of this disease, the bats were popularly regarded as responsible.

In 1911 Carini [1] proved that the disease in cattle was rabies by demonstration of Negri bodies and by inoculation into other animals. There was then practically no canine rabies in this region, and a vigorous campaign in which thousands of dogs were exterminated did not affect the epidemic in the least. Carini suspected that bats were the carriers, but he did not succeed in securing any bats to prove this. In 1916, however, Haupt and Rehaag,[2] who had come to similar conclusions, first demonstrated rabies virus in a bat, Phyllostoma, a fruit-eating species, which was captured while biting a cow. Later Lima and associates [3] in Brazil demonstrated the virus in vampire bats caught under natural conditions, and they showed that vampire bats after inoculation might carry the virus in their saliva for weeks and even months before showing evidence of illness.

Following its recognition in southern Brazil, the infection, or possibly rather the ability to recognize it, spread southward into Uruguay and northern Argentina and gradually northward through Brazil into Venezuela. Although there were repeated epizootics and many human subjects were bitten by the bats, no case of human rabies from this source was recognized on the South American continent.

In 1925 an extensive epizootic of similar character appeared in the cattle in Trinidad, where it was also misdiagnosed, as botulism. In 1929, however, there appeared an epidemic of ascending paralytic myelitis in man which was at first regarded as poliomyelitis although it was invariably fatal.

[1] Carini, A.: Sur une grande epizootie de rage, Ann. Inst. Pasteur **25**: 843, 1911.

[2] Haupt, H., and Rehaag, H.: Durch Fledermaüse verbreitete seuchenhafte Tollwut unter Viehbeständen in Santa Catarina (Süd-Brasilien), Ztschr. f. Infektionskr. d. Haustiere **22**: 104-127, 1921.

[3] Lima, E. de Q.: A transmissão da raiva bovina pelo morcego hematophago *Desmodus rotundus*, Brazil-Med. **48**: 38, 1931.

After 18 cases had occurred, Hurst and Pawan (1932) [4, 5] proved that the disease was rabies, both by demonstrating Negri bodies in the brain and by animal inoculation.

The symptoms in these patients differed from those caused by the usual canine strains of rabies.[4, 6] The incubation period of usually three to four weeks was followed by a brief prodromal period of fever and malaise. Then there was tingling, numbness, disagreeable paresthesias or pain in the limb that was bitten, followed in a day or so by paresis of the muscles of the limb. This quickly extended to the opposite side and progressed to complete paralysis. The process quickly ascended to involve the upper limbs, muscles of deglutition (with salivation) and respiration leading invariably to death from respiratory failure after about seven days. As a rule there was no stage of excitement, no muscle spasm and no "hydrophobia." Often there was retention of urine, constipation and abdominal distention.

During the early period of these epidemics (1931 to 1932), as was the case in Brazil, bats were often observed flying about in the daytime, shrieking, fighting and biting each other as well as the large mammals. The similarity of the paralytic disease in man to that conveyed by the bats to cattle suggested a common origin. Hurst and Pawan [5] demonstrated rabies in the brain of 12 such bats captured while flying. Pawan in 1936 [7, 8] further reported the demonstration of rabies virus in 22 bats examined because of abnormal behavior, and he summarized the evidence convincingly incriminating bats as the vectors of infection in the human cases.

During the period 1929 to 1935, 55 cases of paralytic rabies in man were observed in Trinidad, and it was possible adequately to investigate 40 of these later. In all but one a definite history of a bat bite was obtained, nearly always by a vampire.

The vampire (*Desmodus rotundus murinus*) is a relatively small animal about three inches long with a wing span of 12 to 15 inches. These bats live in fairly large colonies, are nocturnal in their activities, and spend the day hanging head downward from some perch in a dark sheltered place like a hollow tree, a cave, or under the eaves of abandoned buildings. They are agile flyers and walkers. They feed chiefly on cattle, horses or barnyard fowl but will bite man if occasion offers, usually on the feet. They also fight and bite each other, and if one bat becomes infected, the virus is spread through much of the colony.

[4] Hurst, E. W., and Pawan, J. L.: An outbreak of rabies in Trinidad, without history of bites, and with the symptoms of acute ascending myelitis, Lancet **2**: 622-628, 1931.

[5] Hurst, E. W., and Pawan, J. L.: A further account of the Trinidad outbreak of acute rabic myelitis; histology of the experimental disease, J. Path. and Bact. **35**: 301, 1932.

[6] de Verteuil, E., and Urich, F. W.: The study and control of paralytic rabies transmitted by bats in Trinidad, B. W. I., Trans. Roy. Soc. Trop. Med. and Hyg. **29**: 317-347, 1935-36.

[7] Pawan, J. L.: The transmission of paralytic rabies in Trinidad by the vampire bat (*Desmodus rotundus murinus* Wagner, 1840), Ann. Trop. Med. and Parasitol. **30**: 101-129, 1936.

[8] Pawan, J. L.: Rabies in the vampire bat of Trinidad, with special reference to the clinical course and the latency of infection, Ann. Trop. Med. and Parasitol. **30**: 401-422, 1936.

They are blood-lappers, not suckers, slicing into the skin with their sharp chisel-like upper incisors and inflicting a crater like wound about three millimeters in diameter which bleeds freely. An anticoagulant has been described in their saliva. Bites are relatively painless, and sleeping victims are often not awakened. A small animal might be exsanguinated, but large mammals suffer little from the bite if the bats are healthy and do not convey infection.

The fruit-eating and insectivorous bats do not ordinarily ingest blood and do not normally bite other animals unless molested. In fights with vampires, however, they are often bitten and may be infected. A significant number of such fruit-eaters, however, which were captured while biting other animals or exhibiting other types of abnormal behavior, have been found infected with rabies. Their disposition and habits are changed like those of a "mad dog."

The incubation period of rabies in the vampire bat[9] following inoculation may range from a week to several months, usually three to four weeks. There is often a prodromal period of about a day of irritability, restlessness, tremor, or occasionally apathy. This may be followed immediately by a fatal progressive paralysis, but more often by a stage of "fury," lasting one to five days, during which they show excitement and aggressive hostility and may suffer injury by flinging themselves recklessly against and biting the wire network of their cages. Occasionally a bat apparently recovers from this stage although still excreting virus in the saliva. More often it terminates in a paralytic stage which is rapidly fatal. Some bats are refractory, and some may live for months apparently healthy, although excreting virus in the saliva from the seventh day after inoculation. One animal caught under natural conditions was maintained in the laboratory for five and a half months on defibrinated blood and was then sacrificed. Rabies virus was demonstrated in its brain although it had never shown signs of illness. The frequency of rabies carriers among bats during an epidemic period in Trinidad in 1936 was reported by Pawan to be 3.8 per cent of 2,292 captured bats. Four frugivorous and one insectivorous bat were positive.

The disease in Trinidad has since been controlled by suitable public health measures, including the bat-proofing of houses and stables, immunization of live stock, destruction of vampires and protective vaccination.

For 45 years or more a fatal paralytic disease in cattle has been prevalent in the western (Pacific) states of Mexico, known locally as derriengue. Clinically it is identical with the disease described in Brazil and Trinidad. In 1932 Girou obtained a virus from a cow with the paralytic disease which was related to ordinary rabies virus. As canine rabies did not occur in that region and vampire bats had not been discovered, the significance of the observation was not appreciated. In 1948 Johnson[9] investigated the dis-

[9] Johnson, H. N.: Derriengue: vampire bat rabies in Mexico, Am. J. Hyg. 47: 189-204, 1948.

ease more thoroughly. In seven localities in which the disease was prevalent, a search revealed vampire bats in all. He recovered the virus from a dying cow and from pooled brains and salivary glands of vampire bats. This virus was positively identified as rabies, not only by inoculation into animals and demonstration of Negri bodies but also by complement fixation, crossed neutralization and protection tests. Some strain differences have been observed, and the bat virus is possibly slightly less virulent for other animals than the ordinary fixed virus. Vaccination with fixed virus vaccine protects well from bat virus, but vaccine from the latter affords relatively feeble protection from fixed virus.

At that time the infection was known to have extended inland for 100 miles, and since then both the disease and vampire bats have been reported from practically every state in Mexico, including the northern tier bordering on Texas. Similar epizootics have also been reported from Honduras.

Vampire bats have not as yet been reported in this country. Their habits are strictly adapted to a tropical climate, and they are not likely to penetrate significantly into the United States. Their presence in Texas was suspected by Hogan (1951) because of a case of paralytic rabies in a human subject developing three weeks after a bat bite.

In 1954 Sullivan et al.[10] collected 200 bats from central and southern Texas, all colonial insectivorous species, and obtained and positively identified two strains of rabies virus from the Mexican free-tailed bat, *Tadarida mexicana.* These bats migrate into Mexico where they may encounter vampires. Prior to Sullivan's observations, however, Venters et al.[11] demonstrated rabies virus in bats in Florida. The first observation concerned a Florida yellow bat, *Dasypterus floridanus,* an insectivorous species, which flew out of shrubbery on a ranch and bit a child. Routine examination of the bat showed Negri bodies, and the virus was isolated by animal inoculation and identified in the State Laboratory in Jacksonville. The child was immunized and remained well. Venters then collected 208 bats from the ranch and its surroundings within a radius of 25 to 35 miles and obtained six (and a probable seventh) strains of rabies virus. Six were from Florida yellow bats and one from a Seminole bat. These bats are not known to migrate, and the source of their infection is uncertain.

In 1954 an additional case was reported by Witte [12] in Boiling Springs, Pennsylvania, where without provocation a woman was bitten on the arm by a bat. This was captured, Negri bodies were demonstrated, and the disease was conveyed to rabbits by inoculation. The woman was immunized and remained well. The bat was not identified with certainty but was probably a *Lasciurus cinereus,* an insectivorous species which is widely distributed in the United States and up into southern Canada and is known

[10] Sullivan, T. D., et al.: Recovery of rabies virus from colonial bats in Texas, Pub. Health Rep. **69**: 766-768, 1954.
[11] Venters, H. D.: Rabies in bats in Florida, Am. J. Pub. Health **44**: 182-185, 1954.
[12] Witte, E. J.: Bat rabies in Pennsylvania, Am. J. Pub. Health **44**: 186-187, 1954.

to migrate as far south as central Mexico. At the time, late September, they were able to collect only seven other bats, none of which were infected.

In considering the significance of these observations, the questions naturally arise, is this truly rabies, and if so are a few infected bats of much practical significance in temporate climates? The presence of Negri bodies, the results of animal inoculation, serologic reactions, neutralization and protection tests leave no reasonable doubt that the virus is truly rabies. It is somewhat modified, however, quite possibly by passage through the bats. The most striking characteristic is the paralytic type of infection it causes, invariably in man, and almost invariably in cattle, unusual in canine rabies.

It is also surprising that cases of human infection were not recognized either in Brazil or Mexico, although in the former, at least, many human subjects were bitten by vampires, some of which were surely infected. In Trinidad, too, no human case appeared until four years after the epizootics in cattle were recognized. Then abruptly human cases appeared in small recurrent epidemics, suggesting that there had been some abrupt change or mutation of the virus which increased its infectivity for the human host.[8]

As to the bats, the vampires, much the most dangerous species, are not likely to present any direct problem except possibly in southern Texas. It is significant that "harmless" frugivorous and insectivorous bats are frequently bitten and may be infected by the vampires, that they also may carry virus in the brain and excrete it in the saliva for weeks or months before they show evidence of illness, and when they become rabid they may fight, bite and infect each other as well as other mammals, particularly cattle, occasionally man. It may prove significant that rabies has already been found in four species of such bats in the United States, including one which migrates and ranges from Mexico to southern Canada and apparently may survive to carry the infection at least as far north as Pennsylvania.

It seems unlikely that human subjects will be infected directly by the bite of such a bat except as a rare accident. It is more likely that bats may come to constitute an additional reservoir of infection in the wild life of this country. It is conceivable that directly or indirectly they might exchange strains of virus with the dogs and foxes, since such transfer is possible by direct inoculation. In South and Central America, however, thus far rabies in bats epidemiologically has had no relation whatever to canine rabies except perhaps in Venezuela. Whether the strains of rabies virus carried by bats in the United States, like the Trinidad strains, are highly infectious for man is not yet certain, but for the present a bite by an unmolested bat should be regarded as potentially serious. These points can be determined only by further observations, which doubtless will soon be forthcoming.

PAUL W. CLOUGH

REVIEWS

Textbook of Neurology. By H. Houston Merritt, M.D. 746 pages; 15.5 × 24 cm. Lea and Febiger, Philadelphia. 1955. Price, $12.50.

The plan of this book represents a departure from the usual textbook of neurology in that sections on neuroanatomy, neurological examination and topical diagnosis are not presented. The omission of such material has resulted in a more compact volume but has reduced its value somewhat to the medical student and the practicing physician as a complete neurological text. The material presented, however, is that which is most useful to the medical student and the practicing physician since only the more commonly encountered neurological diseases are discussed in considerable detail. The subject matter is discussed according to etiology. The illustrations are adequate. One outstanding feature of the book is the frequent use of tables taken from the literature to present certain aspects of neurological disease. These will be very helpful to the medical student. The sections on treatment of the common neurologic disorders are sufficiently detailed to be of value to the practicing physician. The bibliography at the end of each section in the book is representative of the literature and is up-to-date. The index is quite complete, thus creating a good reference volume. This book which was apparently designed for the medical student and the general practitioner will be most useful to them. The plan of omitting certain aspects from the volume may be criticized but the execution of the plan is above criticism and has resulted in a very worthwhile textbook.

Charles Van Buskirk, M.D.

Rutin and Related Flavonoids: Chemistry, Pharmacology, Clinical Applications. By John Q. Griffith, Jr., M.D., Charles F. Krewson, Ph.D., and Joseph Naghski, Ph.D. 275 pages; 15.5 × 23.5 cm. Mack Publishing Company, Easton, Pennsylvania. 1955. Price, $7.50.

It was announced in 1943 that certain of the flavonoids isolated from plant sources would in some cases restore to normal capillaries with increased fragility. Since the active material was concerned with capillary permeability and was believed at first to be a dietary essential, it was designated as Vitamin P. However, the status of these compounds as vitamins is by no means certain; therefore they should be described as flavonoids rather than as Vitamin P, although in medical literature the latter term is commonly used.

This book presents an evaluation of the clinical research on rutin, its pharmacology and chemistry. The commercial production of rutin from buckwheat is described. In addition, a chapter has been included on the preparation of quercetin from natural sources and the results of some clinical studies with this compound.

The compilation in one volume of the collected information on rutin, with an excellent bibliography, is a commendable undertaking and the authors are to be congratulated upon their thoroughness.

The clinical effectiveness of rutin has been difficult to establish. The authors present evidence which they feel is convincing of the therapeutic effectiveness of rutin in a wide variety of clinical conditions. The Council on Pharmacy and Chemistry of the American Medical Association as long ago as 1950 submitted a skeptical report on the alleged ability of the flavonoid substances to increase capillary resistance. Today the subject remains polemic. There is no direct evidence that the flavonoids are essential in the diet of man. There are many inconsistencies in the literature regarding the absorption of these materials from the gastrointestinal tract. The bulk of the evidence indicates that following oral administration there is no urinary ex-

cretion of unchanged flavonoids or degradation products, while parenteral injection is followed by urinary excretion of unchanged flavonoids. In view of the lack of evidence that the compounds are absorbed, and in light of the frequent reports of negative clinical results following therapy with the flavonoids, one must conclude that their therapeutic usefulness still remains to be established.

It is possible that this monograph may provide a stimulus for additional work. There can be no doubt but that the subject is provocative; perhaps a better knowledge of the rôle of the flavonoids at an enzyme level will be forthcoming, and this in turn may yield a clue as to their rôle in biochemical reactions. Armed with this knowledge the physician would be in a better position to assess their clinical usefulness.

C. JELLEFF CARR

Ciba Foundation Symposium on Leukaemia Research. Editors for the Ciba Foundation: G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., B.Ch., and MARGARET P. CAMERON, M.A., A.B.L.S.; assisted by JOAN ETHERINGTON. 297 pages; 14 × 21 cm. Little, Brown and Company, Boston. 1954. Price, $6.75.

This book represents a compilation of papers which were presented at an international symposium on leukemia research in London in November 1953. Informal discussions are included.

Many well-known investigators participated in this conference, and the material presented is varied. It includes sections dealing with animal neoplasms, mainly leukemias (basic observations as well as a section on the shortcomings of this method of investigation) and several papers concerning newer chemotherapeutic agents directed toward the control of human leukemia. A list of references follows each paper.

Although much of the material in this volume is not new, it is a welcome aggregate under one cover. Both text and discussion material are well presented and easy to read, and sufficient technical information is included. The book would be of interest to anyone concerned with neoplasms, either as a clinical problem or, more especially, from an investigative point of view. The last section, "General Discussion —Where do we go from here? New ideas for research on leukaemia," presents many interesting prospects for study. However, the entire book is thought-provoking and each report suggests numerous unexplored avenues to the interested investigator.

A. M. B.

The Coagulation of Blood: Methods of Study. Edited by LEANDRO M. TOCANTINS, M.D. Prepared with the help and under the sponsorship of the Panel on Blood Coagulation of the Committee on Medicine and Surgery of the National Academy of Sciences, National Research Council. 240 pages; 23.5 × 15.5 cm. Grune & Stratton, New York. 1955. Price, $5.75.

We can only enthusiastically welcome a publication having the characteristics of this book.

Progress in the field of hemorrhagic diseases is such that all the textbooks dealing with the clinical diagnosis by laboratory methods are obsolete in regard to this particular subject.

In spite of advances in this area, the diagnosis of hemorrhagic conditions is often still based upon the methods of whole blood coagulation time, recalcification of plasma, "prothrombin time," impaired prothrombin consumption or prolongation of the whole blood coagulation time. However, today the differentiation of these conditions requires more refined methods. Such methods are now available only in the original descriptions scattered through the literature.

The use of these recent methods in differentiation is not only of academic interest

but can also furnish a basis for better therapy and more precise prognostic evaluation. Tocantins' book now gives us a comprehensive collection of modern diagnostic technics.

This book often describes only one method for the study of each factor involved physiologically or pathologically in the mechanism of coagulation, and this can be considered a defect; but at least this manner of presentation has the advantage of diminishing the space given to theoretic discussions, and it leaves to an expert, the author, the task of choosing the best technic.

The reviewer feels that the P and P method of Owren (Scandinav. Clin. and Lab. Investigation 3: 201, 1951) for the study of prothrombin and proconvertin (SPCA, factor VII) could be more extensively described in this review for its sound basis and the possibility of its being used as a routine test; but the methods described are even more refined, and evidently the purpose of this book is more to satisfy the "coagulationists" than the routine clinical laboratory.

Other methods given here, such as the thromboplastin generation test, are becoming classic.

All in all, this book is as up-to-date in the field of the hemorrhagic disorders as is humanly possible.

G. R.

Physiology and Biochemistry of the Skin. By STEPHEN ROTHMAN, M.D., with contributions by ZACHARY FELSHER, B.A., M.D., PETER FLESCH, M.D., Ph.D., AARON BUNSEN LERNER, M.D., Ph.D., ALLAN L. LORINCZ, M.D., HERMANN PINKUS, M.D., and GEORGE C. WELLS, M.B., M.R.C.P. 741 pages; 17.5 × 25 cm. University of Chicago Press, Chicago, Ill. Price, $19.50.

This text, by a very capable author, fulfills a great need in the realm of dermatology. Dr. Rothman demonstrates the fact that the skin is a very definite organ which has special functions relative to the other life-processes of the body. It is the first text of its kind which deals intimately and adequately with the special functions of the skin and its component parts. It is well written in a fluid style that is easy to read and understand.

The bibliography which follows each chapter is complete. Dr. Rothman has compiled voluminous data on such subjects as the mechanism of wheal formation in urticaria, the innervation of the skin, circulation of the skin, sweat composition, and other functions which are carefully explained with emphasis on the biological meaning of the data. It is without any hesitancy that the reviewer recommends this text to the students in dermatology.

H. M. R., JR.

Ultrasonic and Ultrashort Waves in Medicine. By JOHANNA M. VAN WENT, M.D., Director, Institute for Physical Medicine and Rheumatism, Amsterdam; Introduction by KENNETH PHILLIPS, M.D., F.A.C.P., Director, Parkway Medical Clinic, and Dept. Physical Medicine, Jackson Memorial Hospital, Miami, Florida. 384 pages; 15.5 × 23.5 cm. Elsevier Publishing Company, Amsterdam, Houston, London, New York. 1954. Price, $9.00.

Dr. van Went's book cannot be compared as it is the first of its kind in the field. It presents ultra-sound and ultra-short waves from the point of view of cell stimulation. How much is good for the type of disease? How much is good for the individual patient? Is the patient's resistance so far lowered that cell stimulus may be irreversible? Part one deals with ultra-sound. Part two covers ultra-short wave for hyperthermia and irradiation of the hypophysis. The last division deals with microwaves. All discussions are presented.

This review will concern itself chiefly with ultra-sound only because that is least developed in America and this authoritative presentation should be read by anyone seeking understanding of a new modality or for comparing technics for those who already use ultra-sound. One cannot escape an analogy to early x-ray equipment and experiments.

The brief but exciting history of ultra-sound, the discussion of the contraction principle versus the electro piezo principle, the latter chiefly exemplified in modern sound heads or sonators, the early American and European experience with ultra-sonic waves; dosage and contact problems, properties and effects; these take up the first four chapters.

Biological experiments on plant and animal life with various powers of ultra-sound, provoke much thought. Thermal effects were ruled out in some cases by a water bath, and a standstill of movement in Daphnia was observed reaching from moving external parts to the eyes and heart. The time element has been generously studied and effects noted by named research teams. Changes in nuclei and the chromosomes have been recorded. Dr. van Went's comments on these investigations quoted are shrewd and penetrating. Out of her own large experience as Director of Physical Medicine and Rheumatism, Institute of Amsterdam, she discusses diseases amenable to ultra-sonic irradiation. Her approach is both broad and precise.

For clear and precise information concerning ultra-sound or short wave or hyperthermia or irradiation of the hypophysis, or microwaves we commend the book and no less the bibliography of world research in five languages. There is a subject index of seven pages. Our tribute to Dr. van Went for her patient review of world literature in these comparatively new fields and for the sharp focus of her intelligence lighting up dark corners.

G. E. S.

Pediatric Diagnosis. By MORRIS GREEN, M.D., and JULIUS B. RICHMOND, M.D. 436 pages; 17 × 26 cm. W. B. Saunders Company, Philadelphia. 1954. Price, $10.00.

This book is an interesting excursion into a fresh field. In presenting the art of pediatric diagnosis it begins with the symptom or sign and suggests avenues of reasoning which may lead to the diagnosis. This approach is used in the familiar diagnostic indexes, which deal mainly with adult medicine, but it is not emphasized in the textbooks of pediatrics. This is the approach which physicians must use in seeking a diagnosis: books like this can help one to formulate one's mental catalogue of symptoms. Most of the facts in the book can be found elsewhere, though presented in a different order, but on almost every page are a few unfamiliar ideas.

Only clinical diagnosis is discussed. Laboratory findings are mentioned briefly. On the other hand subjects outside the field of diagnosis are described, for example therapy, pathophysiology, and even isolation procedures. There is also a large chapter on health supervision. The book is printed poorly in the fashionable two-column form. The reader's eye is interrupted frequently by references in fine print inserted between the sentences of the text.

Because of the large amount of accessible information, pediatricians may be glad to keep the book at hand for help with diagnostic problems. Teachers can refer to its many examples of diagnostic reasoning.

G. S. C.

BOOKS RECEIVED

Books received during April are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Brucelosis. By DR. M. RUIZ CASTAÑEDA, Director del Departamento de Investigaciones Medicas, Hospital General, México, D. F., etc. 302 pages; 23.5 × 16 cm. 1954. La Prensa Medica Mexicana, México, D. F. Price, $5.00.

Cardiac Emergencies and Heart Failure: Prevention and Treatment. 2nd Ed. By ARTHUR M. MASTER, M.D., Cardiologist, Mount Sinai Hospital, New York, N. Y., etc.; MARVIN MOSER, M.D., Assistant Physician in Medicine, Montefiore Hospital, N. Y., etc.; and HARRY L. JAFFE, M.D., Assistant Attending Physician, Cardiology, Mount Sinai Hospital, New York, N. Y., etc. 203 pages; 20.5 × 13.5 cm. 1955. Lea & Febiger, Philadelphia. Price, $3.75.

The Cerebrospinal Fluid. By S. LUPS, M.D., Medical Director, Municipal Hospital, Rotterdam, etc.; and A. M. F. H. HAAN, M.D., Head of the Biochemical, Cytological and Bacteriological Laboratory, Sanatorium "Oranje Nassau's Oord," Renkum (The Netherlands); with an introduction by PEARCE BAILEY, M.D., Director, National Institute of Neurological Diseases and Blindness, Bethesda, Md. (U. S. A.). 350 pages; 23.5 × 15.5 cm. 1954. Elsevier Publishing Company, Houston, Texas. Price, $9.50.

Clinical Disorders of Hydration and Acid-Base Equilibrium. By LOUIS G. WELT, M.D., Professor of Medicine, Department of Medicine, University of North Carolina. 262 pages; 22 × 14.5 cm. 1955. Little, Brown & Company, Boston. Price, $6.00.

Cold Injury: Transactions of the Third Conference, February 22, 23, 24 and 25, 1954, Fort Churchill, Manitoba, Canada. Edited by M. IRENÉ FERRER, M.D., Assistant Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons, New York, N. Y. 226 pages; 23.5 × 16 cm. 1955. Sponsored by the Josiah Macy, Jr. Foundation, New York, N. Y. Price, $4.50.

Differential Diagnosis of Internal Diseases: Clinical Analysis and Synthesis of Symptoms and Signs on Pathophysiologic Basis. 2nd Ed. By JULIUS BAUER, M.D., F.A.C.P., Clinical Professor of Medicine, College of Medical Evangelists, Los Angeles, etc. 987 pages; 23.5 × 15.5 cm. 1955. Grune & Stratton, Inc., New York. Price, $15.00.

Diseases of the Thyroid Gland. By SAMUEL GARGILL, M.D., Assistant Clinical Professor of Medicine, Harvard Medical School, etc.; and MARK FALCON LESSES, M.D., Instructor in Medicine, Harvard Medical School, etc. Reprinted from *Oxford Loose-Leaf Medicine* with the same page numbers as in that work; 24.5 × 18 cm. 1955. Oxford University Press, New York. Price, $12.00.

La Electricidad, Alma Mater Universal: Fenómenos Cosmológicos y Biopsicológicos. Tomo I. By ALICE LARDÉ DE VENTURINO. 126 pages; 22 × 16 cm. (paper-bound). 1954. Editorial Cervantes, Barcelona.

La Electricidad en los Fenomenos Bio y Psicologicos: Amor o Atraccion Espiritu-Sexual Herencia, Vigor, Rejuvenecimiento de los Ancianos Vejez Precoz, Locura Profesional y Otros Fenomenos Psiquicos y Organicos Inducidos. II Parte. By ALICE LARDÉ DE VENTURINO. 256 pages; 22 × 16 cm. (paper-bound). 1954. Editorial Cervantes, Barcelona.

Expert Committee on Drugs Liable to Produce Addiction: Fifth Report. World Health Organization Technical Report Series No. 95. 16 pages; 24 × 16 cm. (paper-bound). 1955. World Health Organization, Geneva; available through Columbia University Press, International Documents Service, New York. Price, 30¢.

Fluoroscopy in Diagnostic Roentgenology. By OTTO DEUTSCHBERGER, M.D., Assistant Clinical Professor of Radiology, New York Medical College, etc.; with an introduction by FRANK J. BORRELLI, M.D., F.A.C.R., Professor of Radiology, New York Medical College, etc. 771 pages; 26 × 18 cm. 1955. W. B. Saunders Company, Philadelphia. Price, $22.00.

Foetal, Infant and Early Childhood Mortality. Volume I. The Statistics. Population Studies, No. 13. 137 pages; 28 × 21.5 cm. (paper-bound). 1954. Department of Social Affairs, Population Division, United Nations, New York; available from International Documents Service, Columbia University Press, New York. Price, $1.50.

Foetal, Infant and Early Childhood Mortality. Volume II. Biological, Social and Economic Factors. Population Studies, No. 13. 44 pages; 28 × 21.5 cm. (paper-bound). 1954. Department of Social Affairs, Population Division, United Nations, New York; available through International Documents Service, Columbia University Press, New York. Price, 40¢.

Gestation: Transactions of the First Conference, March 9, 10 and 11, 1954, Princeton, N. J. Edited by LOUIS B. FLEXNER, M.D., Professor and Chairman, Department of Anatomy, University of Pennsylvania School of Medicine, Philadelphia, Pa. 238 pages; 23.5 × 16 cm. 1955. Sponsored by the Josiah Macy, Jr. Foundation, New York, N. Y. Price, $5.00.

Heart Disease: Its Diagnosis and Treatment. 2nd Ed. By EMANUEL GOLDBERGER, M.D., F.A.C.P., Associate Attending Physician, Montefiore Hospital, New York, etc. 781 pages; 24 × 15.5 cm. 1955. Lea & Febiger, Philadelphia. Price, $12.50.

Hematology. 2nd Ed. By CYRUS C. STURGIS, M.D., Professor of Internal Medicine, Chairman of the Department of Internal Medicine, University of Michigan Medical School, etc. 1,222 pages; 26.5 × 16.5 cm. 1955. Charles C Thomas, Publisher, Springfield, Illinois. Price, $19.50.

Immunity and Hypersensitivity, Relationship to Disease in Man: Report of the Ninth M & R Pediatric Research Conference. 79 pages; 23 × 15.5 cm. (paper-bound). 1955. M & R Laboratories, Columbus, Ohio. Available to the medical profession without charge.

Klinische Zytologie der Thoraxkrankheiten. By HEINZ GRUNZE; with directions for obtaining material by HANS-JURGEN BRANDT, and comment by HANS SCHULTEN. 190 pages; 26 × 18 cm. 1955. Ferdinand Enke Verlag, Stuttgart. Price, Geheftet DM 56.–; ganzleinen DM 59.–.

Letalfaktoren in Ihrer Bedeutung für Erbpathologie und Genphysiologie der Entwicklung. By ERNST HADORN. 338 pages; 24.5 × 17.5 cm. 1955. Georg Thieme Verlag, Stuttgart; available in the U. S. A. and Canada from Intercontinental Medical Book Corporation, New York. Price, Ganzleinen DM 39.–.

Management of Addictions. By EDWARD PODOLSKY, M.D., Department of Psychiatry, Kings County Hospital, Brooklyn, New York. 413 pages; 22 × 14 cm. 1955. Philosophical Library, New York. Price, $7.50.

Methods for Evaluation of Nutritional Adequacy and Status: A Symposium Sponsored by the Quartermaster Food and Container Institute for the Armed Forces Quartermaster Research and Development Command, U. S. Army Quartermaster Corps and Medical Nutrition Laboratory, Research and Development Division,

Office of the Surgeon General, Oriental Institute, University of Chicago, February 25–26, 1954. Edited by HARRY SPECTOR and MARTIN S. PETERSON, Quartermaster Food and Container Institute, for the Armed Forces, Chicago, and T. E. FRIEDEMANN, Medical Nutrition Laboratory, Office of the Surgeon General. 313 pages; 23.5 × 15 cm. (paper-bound). 1955. Copies are available at the Quartermaster Food and Container Institute for the Armed Forces, 1819 West Pershing Road, Chicago-9, Illinois. Price: Copies distributed without charge to those concerned with research in this field who may need to know or to refer to the studies reported in these proceedings.

Multiple Sclerosis. By DOUGLAS MCALPINE, M.D., F.R.C.P., Physician-in-Charge of Department for Nervous Diseases, The Middlesex Hospital, London, etc.; NIGEL D. COMPSTON, M.A., M.D. (Cantab.), M.R.C.P., Assistant Physician, The Royal Free Hospital and Hampstead General Hospital, London, etc.; and CHARLES E. LUMSDEN, M.D. (Aberd.), Sir Henry Head Research Fellow of the Royal Society, etc. 304 pages; 24.5 × 15.5 cm. 1955. The Williams & Wilkins Company, Baltimore. Price, $7.00.

Neurology. 2nd Ed. (in three volumes). By S. A. KINNIER WILSON, M.A., M.D., D.Sc. (Edin.), F.R.C.P., Formerly Physician, National Hospital, Queen Square, etc.; edited by A. NINIAN BRUCE, F.R.C.P. (Edin.), D.Sc. (Edin.), M.D., F.R.S. (Edin.), Lt.-Col. R.A.M.C., Consulting Physician, Bangour Mental Hospital and St. Andrew's Hospital, Hawick, etc. 2,212 pages; 25 × 17 cm. 1955. The Williams & Wilkins Company, Baltimore. Price, $37.50.

1955 Medical Progress: A Review of Medical Advances During 1954. MORRIS FISHBEIN, M.D., Editor. 346 pages; 23.5 × 15.5 cm. 1955. The Blakiston Division, McGraw-Hill Book Company, Inc., New York. Price, $5.00.

Pathology. By PETER A. HERBUT, M.D., Professor of Pathology, Jefferson Medical College, and Director of Clinical Laboratories, Jefferson Medical College Hospital, Philadelphia, Pennsylvania. 1,227 pages; 26.5 × 18 cm. 1955. Lea & Febiger, Philadelphia. Price, $16.00.

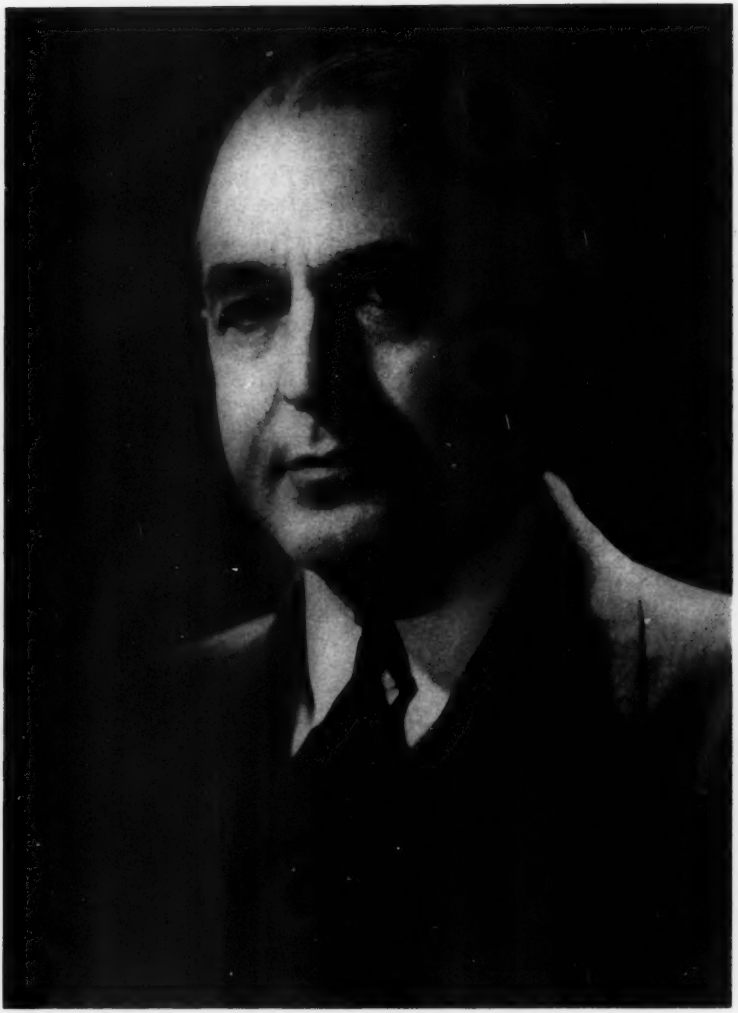
Pomp and Pestilence: Infectious Disease, Its Origins and Conquest. By RONALD HARE, M.D., Professor of Bacteriology in the University of London at St. Thomas's Hospital Medical School. 224 pages; 20.5 × 13 cm. 1955. The Philosophical Library, Inc., New York. Price, $5.75.

Reflections on Renal Function. By JAMES R. ROBINSON, M.D., Ph.D. (Cantab.), Assistant Director of Research, Department of Experimental Medicine, Medical Research Council and University of Cambridge, etc. 163 pages; 22.5 × 14.5 cm. 1955. Charles C Thomas, Publisher, Springfield, Illinois. Price, $3.50.

The Tubercle Bacillus in the Pulmonary Lesion of Man: Histobacteriology and Its Bearing on the Therapy of Pulmonary Tuberculosis. (Enlarged and revised edition of *"Le bacille de Koch."*) By GEORGES CANETTI, M.D., Director of Laboratory, Pasteur Institute, Paris; foreword by RENE J. DUBOS and WALSH MCDERMOTT. 226 pages; 23.5 × 15.5 cm. 1955. Springer Publishing Company, Inc., New York. Price, $8.50.

ERRATUM

January, 1955, page 148, lines 9 and 10 should read, "rate of deaths from Hodgkin's disease has risen from 11 per million in 1930 to 17 per million in 1949."



GEORGE FREDERIC STRONG, B.S., M.D., F.A.C.P., F.R.C.P.(C)
PRESIDENT
AMERICAN COLLEGE OF PHYSICIANS

George Frederic Strong, 925 Georgia St., W., Vancouver, B. C., Can. Born, February 22, 1897, St. Paul, Minn. B.S., 1918, University of Minnesota; M.D., 1921, University of Minnesota Medical School. Resident and Postgraduate Training, 1922–23, Peter Bent Brigham Hospital, Boston, and Fellowship under the National Research Council. For many years, Director of EKG Department and Physician to the Outpatient Cardiac Clinic, Vancouver General Hospital; since 1946, Chief of the Department of Medicine and presently Senior Attending Physician, Vancouver General Hospital; since 1951, Clinical Professor of Medicine, University of British Columbia Faculty of Medicine; author of numerous medical articles and essays; successively Secretary, Vice President, and President, Vancouver Medical Association; successively Vice President and President, British Columbia Medical Association; Past President, North Pacific Society of Internal Medicine; member, Pacific Interurban Clinical Club and Canadian Medical Association; Fellow, Royal College of Physicians and Surgeons of Canada; Diplomate, American Board of Internal Medicine; Fellow (1937), American College of Physicians; A.C.P. Governor for the Provinces of Alberta, British Columbia, Manitoba, and Saskatchewan, 1940–44; Regent of the College, 1944–48; First Vice President, 1949–50 and 1953–54.

Dr. Strong was elected President-Elect of the American College of Physicians at the Chicago Annual Session, April 8, 1954 and was installed as President at the Philadelphia Annual Session, April 28, 1955.

WALTER LINCOLN PALMER, B.S., M.S., M.D., Ph.D., F.A.C.P.
PRESIDENT-ELECT
AMERICAN COLLEGE OF PHYSICIANS

Walter Lincoln Palmer, 950 E. 59th St., Chicago, Ill. Born, June 29, 1896, Evanston, Ill. B.S., 1918 and M.S., 1919, University of Chicago; M.D., 1921, Rush Medical School; Ph.D., 1926, University of Chicago. Resident and Postgraduate training, Cook County and Presbyterian Hospitals, Chicago; European training in Vienna, Munich and Berlin, 1926–27; Fellowship in Medicine, University of Chicago, 1927–29. University of Chicago School of Medicine: Assistant Professor of Medicine, 1927–30; Associate Professor of Medicine, 1930–41; Professor of Medicine since 1941. Chairman and Diplomate, American Board of Internal Medicine.

The American College of Physicians: Fellow, 1939; Governor for Northern Illinois, 1944–51; Regent since 1951; Member of Committee on Finance, the Committee on Fellowships and Awards, the Executive Committee and Chairman of the Joint Committee for the Co-ordination of Medical Activities and the Editorial Board; President-Elect, 1955–56.

Dr. Palmer was elected President-Elect of the American College of Physicians at the Philadelphia Annual Session, April 28, 1955, and will serve as President 1956–57.

COLLEGE NEWS NOTES

New Life Members

The College is pleased to announce that the following Fellows have become Life Members since the publication of the May issue of this journal:

Dr. Augustus R. Felty, Hartford, Conn.
Dr. Joseph F. Paulonis, Brooklyn, N. Y.
Dr. John M. Higgins, Sayre, Pa.
Dr. Raphael J. Condry, Elkins, W. Va.
Dr. Ralph W. Trimmer, Oak Park, Ill.
Dr. Elwood A. Sharp, Detroit, Mich.
Dr. E. C. Robichaux, Excelsior Springs, Mo.

Gifts to College Library of Publications by Members

The College is indeed grateful to Dr. William B. Terhune, M.D., F.A.C.P., New Canaan, Conn., for presenting an autographed copy of his recently published *Emotional Problems and What You Can Do About Them* to the College Library of Publications by Members.

Ninth Annual Rocky Mountain Cancer Conference

The Ninth Annual Rocky Mountain Cancer Conference, sponsored by the Colorado State Medical Society and the Colorado Division of the American Cancer Society, will be held at Denver, July 13–14.

Among the speakers will be Dr. William Dock, F.A.C.P., Brooklyn, who will participate in a Symposium on Carcinoma of the Respiratory Tract and will present a formal paper. Other guests participating will be Drs. Elmer Hess, President-Elect, A.M.A., Urology; J. Neerman Nesselrod, Proctology, Evanston; David A. Wood, Pathology, San Francisco; Harry M. Nelson, Gynecology, Detroit; Wendell G. Scott, Radiology, St. Louis; Joel J. Pressman, Eye, Nose and Throat, Los Angeles; and Louis Thomas Byars, Plastic Surgery, St. Louis.

Additional details may be obtained from Frederick H. Brandenburg, M.D., Chairman, Committee on Cancer Conference, 835 Republic Building, Denver 2, Colo.

Motion Picture Films

A completely revised Fourth Edition of *Professional Films* is now in compilation by the Academy-International of Medicine. (The frequency and number of future insert pages necessary to assure a comprehensive index that is continuously current over a period of years will be determined by the volume of forthcoming productions.) It will include new sections providing biographical data on authors and information on the audio-visual activities of medical schools, dental schools and postgraduate teaching centers.

Over 28,000 copies of previous editions are in use by medical and dental schools, Program Chairmen of State and specialty societies, and others here and abroad. Academy-International of Medicine provides this valuable audio-visual information to the profession-at-large, without profit, as one of its contributions toward elevating the standards of medical and dental services by expediting the disseminating of professional knowledge.

Film authors are urged to provide their film title and their full name and address to the Academy-International of Medicine, 601 Louisiana St., Lawrence, Kansas.

Dr. Ernest E. Irons, M.A.C.P., Chicago, was singularly honored by the Chicago Junior Association of Commerce and Industry for his distinguished service as President of the Board of Directors of the Municipal Tuberculosis Sanitarium of Chicago. He was given the Jaycee's Good Government Award for 1955, the purpose of which is "to recognize and acclaim those public servants who have rendered outstanding service to the people of Chicago and Cook County and by this means, to help raise the morale of our public officeholders and contribute to an over-all increase in the efficiency of public agencies. . . ."

Dr. W. Barry Wood, Jr., F.A.C.P., St. Louis, has been named Vice President both of Johns Hopkins University and Johns Hopkins Hospital. He was formerly Professor of Medicine and head of that department at the School of Medicine, Washington University, St. Louis. In his new post, Dr. Wood will be Coördinating Officer for the Hospital, the School of Medicine and the School of Hygiene and Public Health, the three units comprising the Johns Hopkins Medical Center.

Dr. W. T. Thompson, Jr., F.A.C.P., Richmond, is the newly elected President of the Virginia Association of Mental Health.

Dr. Charles B. Sanders, F.A.C.P., Houston, was recently made President of the Texas Society of Pathologists, Inc.

Dr. David Gelfand, F.A.C.P., Philadelphia, has been promoted to Assistant Professor (Cardiology) at the Graduate School of Medicine, University of Pennsylvania.

Dr. Hugh R. Leavell, F.A.C.P., Cambridge, has been elected President of the National Health Council. The Council is made up of representatives from the leading national health and medical organizations.

Two Fellows of the College, Dr. William W. Bondurant, Jr., San Antonio, and Dr. DeWitt Neighbors, Fort Worth, have been elected President and Vice President, respectively, of the Texas Academy of Internal Medicine.

Dr. Thurman Crawford, F.A.C.P., Memphis, was made Secretary of the Mid-South Postgraduate Medical Assembly at its annual convention in Memphis.

Three members of the College participated in the 67th Annual Meeting of the American Association of Railway Surgeons, held in Chicago, April 12–14. Dr. Steven O. Schwartz, F.A.C.P., Chicago, discussed "Hypersplenism and the Anemias," and Drs. LeRoy H. Sloan, F.A.C.P., a Past President of the College, and Don C. Sutton, F.A.C.P., both of Chicago, spoke, respectively, on "Therapy of Hypertension" and "Diagnosis and Treatment of Coronary Thrombosis."

Drs. Kenneth A. Evelyn, F.A.C.P., and Bram Rose, F.A.C.P., both of Montreal, took part in a Symposium on Modern Trends in Treatment, which was sponsored by the Manitoba Medical Association, University of Manitoba Faculty of Medicine, together with Lederle Laboratories, and was held in Winnipeg on April 4. Their rspective subjects were "Modern Treatment of Hypertension" and "Recent Advancements in the Treatment of Allergic Disorders."

Dr. Ivan F. Duff (Associate), Ann Arbor, Mich., recently spoke on "Joint Fluid Changes Induced by Systemic and Local Administration of Steroids" at the University of Wisconsin Medical School, Madison. The lecture was sponsored by the Alpha Omega Alpha fraternity.

Dr. Mandred W. Comfort, F.A.C.P., Rochester, Minn., discussed "Early Detection of Cancer. Early Diagnosis of Cancer and the Survival Rates" at the Fourth Annual State Tumor Conference in Wichita Falls, Tex., on April 6.

Dr. Priscilla White, F.A.C.P., Boston, delivered the Eighth Annual Lectureship of the Mu chapter of Phi Delta Epsilon Fraternity at Jefferson Medical College of Philadelphia on April 4. Her subject was "Pregnancy Complicating Diabetes."

Five members of the College contributed to the program of the Seventh Meeting of the New York Cancer Society (Sixth National Gastrointestinal Cancer Conference), held at the New York Academy of Medicine, April 4–5. Dr. H. Marvin Pollard, F.A.C.P., Ann Arbor, College Governor for Michigan, presented "Natural History of Survival in Carcinoma of the Stomach, Treated and Untreated." Dr. W. Edward Chamberlain, F.A.C.P., Philadelphia, discussed "Use of Image Tubes and Amateur Photographic Equipment to Reduce Exposure to Radiation at Fluoroscopy," and Dr. Harry L. Segal, F.A.C.P., Rochester, N. Y., spoke on "Present Status and Trend of Ion Exchange Tubeless Determinants of Gastric Acidity." The respective subjects of Drs. Seymour J. Gray, F.A.C.P., Boston, and George B. Jerzy Glass (Associate), New York City, were "Clinical Use of the Urinary Uropepsin Excretion in Distinguishing Benign Lesions from Malignant Gastric Cancer" and "Intestinal Absorption of Radioactive Vitamin B_{12} in Patients with Cancer of the Stomach Following Subtotal and Total Gastrectomy."

Drs. William Likoff, F.A.C.P., Philadelphia, and Joe W. Howland (Associate), Rochester, N. Y., were among the out-of-state speakers at a Symposium on Recent Advances in Medicine, presented by the Louisiana Academy of General Practice and held in New Orleans, April 17. Their respective discussions were "Cardiac Auscultation" and "Future of Atomic Energy in Medicine."

Dr. Isidore Snapper, F.A.C.P., Brooklyn, presented a refresher course, "Classification and Clinical Manifestations of Systemic Bone Diseases," during the Fifth Inter-American Congress of Radiology held in Washington, D. C., April 24–29. Dr. Eugene P. Pendergrass, F.A.C.P., Philadelphia, was Secretary General of the Congress.

Dr. Esmond R. Long, F.A.C.P., Philadelphia, presented the annual Clendening Lectures on the History and Philosophy of Medicine at the University of Kansas Medical School in Lawrence, April 12–13. On Tuesday Dr. Long presented "The Illness and Medical Care of Frederic Chopin," and on Wednesday his subject was "The Therapy of Tuberculosis from Hippocrates to Modern Times."

Out-of-state speakers and their subjects at a Symposium on Treatment of Cardiovascular Disease, sponsored by the Stamford (Conn.) Heart Association and held April 19, included Dr. John P. Merrill, F.A.C.P., Boston, "Diuretic Agents and Their Mechanisms"; Dr. Arthur C. DeGraff, F.A.C.P., New York City, "Use of Digitalis and the Cardiac Glycosides," and Dr. Samuel A. Levine, F.A.C.P., Boston, "Pitfalls in the Treatment of Cardiovascular Disease."

Three Fellows of the College contributed to the spring schedule of lectures sponsored by the House Officers' Association, Boston City Hospital. On April 28, Dr. William A. Sodeman, F.A.C.P., Columbia, Mo., spoke on "Acute Pericarditis: Diagnostic Problems"; on May 10, Dr. Garfield G. Duncan, F.A.C.P., Philadelphia, on "Undernutrition as a Clinical Problem"; and on May 24, Dr. William Dock, F.A.C.P., Brooklyn, on "Diagnostic Value of Tracings of Heart Sounds and Pulsations."

Recent guest speakers of the Hartford (Conn.) Medical Society included Dr. Thomas A. Warthin, F.A.C.P., Boston, "Gastrointestinal Bleeding," and Dr. Louis A. Soloff, F.A.C.P., Philadelphia, "Medical Aspects of Mitral Commissurotomy."

Dr. Matthew T. Moore, F.A.C.P., Philadelphia, discussed "The Diagnosis and Treatment of Subdural Hemorrhage in the Aged" at the annual meeting of the American Geriatrics Society, which met in New York City, April 22–23.

Dr. Cornelius P. Rhoads, F.A.C.P., New York City, was one of the out-of-state speakers at the Tenth Annual Cancer Day presented by the Genesee County Medical Society and held April 13 in Flint, Mich. "Ten Years of Progress with the Cancer Problem" was the topic he discussed.

Capt. William M. Silliphant, (MC), USN, F.A.C.P., Washington, D. C., spoke on the "Pathology of War Wounds" before the members of the surgical staff and the third-year medical students of Baylor University, Houston, Tex., on April 6.

Guest speakers and their discussions at the 163rd Annual Meeting of the Connecticut State Medical Society included: Dr. Frederic D. Zeman, F.A.C.P., New York City, "Practical Problems in the Care of the Aged"; Dr. Harold D. Levine, F.A.C.P., Boston, "Nonspecificity of the Electrocardiogram in Coronary Artery Disease"; Dr. Darrell C. Crain, Jr., F.A.C.P., Washington, D. C., "Brachial Neuralgia—What Is It or Is It?" Dr. Solomon Silver, F.A.C.P., New York City, "Present Day Management of Hyperthyroidism," and Dr. Gene H. Stollerman (Associate), Irvington-on-Hudson, N. Y., "Hormones in Management of Rheumatic Fever."

In the Section on Radiology, Dr. Daniel S. Ellis (Associate), Brookline, Mass., spoke on "Clinical and Roentgen Diagnosis of Right Upper Quadrant Syndromes: Medical Aspect." At the meeting of the Connecticut Trudeau Society, Dr. Maurice S. Segal, F.A.C.P., Boston, discussed "The Use of ACTH and Cortisone in the Treatment of Pulmonary Disease," and Dr. Robert P. McCombs, F.A.C.P., Boston, presented "Systemic Manifestations of Hypersensitivity—Vascular Allergies and the Collagen Diseases" before the Connecticut Allergy Society. At the meeting of the Connecticut Diabetes Association, Dr. Henry Dolger, F.A.C.P., New York City, discussed "Fructose in Diabetic Emergencies," and Dr. Claude-Starr Wright, F.A.C.P., Columbus, Ohio, contributed to that part of the program arranged by the Connecticut Society of American Board of Surgeons. His subject was "The Spleen—Friend or Foe?"

Three members of the College were among the out-of-state speakers at a Symposium on Gastrointestinal Diseases, presented jointly by the Delaware Academy of General Practice and the University of Delaware and held April 16 in Wilmington. Dr. Abraham H. Aaron, F.A.C.P., Buffalo, spoke on "Acute Ulcerative Enteritis"; Dr. Edward A. Marshall, F.A.C.P., Cleveland, discussed "Treating Peptic Ulcers

with Unrestricted Diet"; and Dr. Edward Weiss, F.A.C.P., Philadelphia, presented "Emotional Factors in Gastrointestinal Disorders."

Dr. Louis N. Katz, F.A.C.P., Chicago, delivered the Sixth Annual Lecture presented by the Alpha Eta chapter of Phi Delta Epsilon fraternity at the University of Southern California School of Medicine, Los Angeles. His talk, which was presented April 15, was entitled "Some Recent Trends in Atherosclerosis."

Dr. Herman J. Moersch, F.A.C.P., Rochester, Minn., discussed "Current Advances in the Diagnosis and Treatment of Cardiospasm and Hiatal Hernia" at the annual meeting of the Medical Association of the State of Alabama, held in Montgomery, April 21–23.

Among the guest speakers at the annual session of the Iowa State Medical Society, which convened in Des Moines, April 24–27, was Dr. Harold C. Lueth, F.A.C.P., Evanston, Ill. His subject was "Emergency Medical Service in a Disaster."

Dr. Roscoe L. Pullen, F.A.C.P., Columbia, Mo., presented the Nineteenth Annual Noble P. Sherwood Lecture, "Why Train for General Practice?" at the University of Kansas, Lawrence, on April 20. The lectureship was sponsored by the Alpha Iota Chapter of Phi Beta Pi fraternity.

Drs. James O. Ritchey, F.A.C.P., Indianapolis, and Howard F. Root, F.A.C.P., Boston, were among the principal speakers at a meeting of the Kentucky Chapter of the American Academy of General Practice, which was held in Louisville, April 20–21. Their respective subjects were "Thromboembolism" and "Emergencies in Diabetes."

At the Second Annual Surgical Seminar, sponsored by the Third (B.U.) Surgical Service of the Boston City Hospital and held April 22, Dr. A. Wilbur Duryee, F.A.C.P., New York City, discussed "Medical Management of Arterial Occlusive Disease."

Dr. Garfield G. Duncan, F.A.C.P., Philadelphia, was one of the principal guest speakers at the annual meeting of the Ohio State Medical Association, which met April 19–22, in Cincinnati. At the general session, Dr. Duncan spoke on "The Therapy Spectrum in the Management of Essential Hypertension"; and during the meeting of the Section on Internal Medicine, he presented "Practical Considerations in the Management of Diabetes."

At the 63rd Annual Meeting of the Pennsylvania Tuberculosis and Health Society, which met in Pittsburgh, April 20–22, Dr. J. Arthur Myers, F.A.C.P., Minneapolis, discussed "The Value of the Tuberculin Test." Fellows of the College from Pennsylvania who also participated in the program included Drs. Thomas Parran, Pittsburgh, and Katherine R. Boucot and David A. Cooper, both of Philadelphia.

Under the Presidency of Dr. Howard D. J. Fabing, F.A.C.P., Cincinnati, the American Academy of Neurology held its Seventh Annual Meeting in Houston, Tex., April 25–30. Participating in a symposium, "What We Need to Know About Central Nervous System Vascular Disease," were Dr. Clark H. Millikan, F.A.C.P., Rochester, Minn., Dr. Irvine H. Page, F.A.C.P., Cleveland, and Dr. Adolph L. Sahs, F.A.C.P., Iowa City.

At the 75th Annual Meeting of the American Dermatological Association, held in Belleair, Fla., April 18–21, Dr. Walter C. Lobitz, Jr., F.A.C.P., Hanover, N. H., presented "Histochemical Evidence for Human Eccrine Sweat Duct Activity."

Dr. James R. Shaw, F.A.C.P., Washington, D. C., Chief of the Branch of Public Health, Bureau of Indian Affairs, was a guest speaker at the 22nd Annual Meeting of the Western Branch of the American Public Health Association, which convened in Phoenix, Ariz., April 19–22. On April 21, Dr. Shaw discussed "Transition of Health Services of Indian Service to Public Health Service."

Among the out-of-state speakers at a meeting of the Wisconsin Chapter of the American College of Chest Physicians that was held May 1 in Milwaukee were Drs. J. Arthur Myers, F.A.C.P., Minneapolis, Arthur M. Olsen, F.A.C.P., Rochester, Minn., and George L. Waldbott, F.A.C.P., Detroit. Their respective subjects were, "Clinical Aspects of Pleurisy with Effusion," "Prognosis of Bronchiectasis," and "Appraisal of Routine Treatment of Bronchial Asthma."

Dr. Henry L. Bockus, F.A.C.P., Philadelphia, delivered the Eighth Annual Eben J. Carey Memorial Lecture on April 21 at Marquette University School of Medicine, Milwaukee. His talk, which was sponsored by the Marquette Chapter of Phi Delta Epsilon International Medical Fraternity, was entitled "Present Status of Medical Management of Peptic Ulcer."

Drs. William J. Kerr, M.A.C.P., San Francisco, and Francis J. Braceland, F.A.C.P., Hartford, Conn., were among the out-of-state speakers who contributed to the 88th Annual Session of the Texas Medical Association. Dr. Kerr presented "The Hyperventilation Syndrome in Clinical Medicine," and Dr. Braceland discussed "Anxiety and Depression as Seen in General Practice." The meeting was held April 24–27 in Fort Worth.

Included as panel moderators at the Twelfth Annual Meeting of the American Geriatrics Society in New York City, April 21–22, were Drs. Laurance W. Kinsell, F.A.C.P., Oakland, Calif., "Diabetes in the Aged"; Charles T. Stone, Sr., F.A.C.P., Galveston, Tex., "Cardiac and Circulatory Diseases"; and Cornelius P. Rhoads, F.A.C.P., New York City, "Cancer."

Dr. Michael L. Matte (Associate), has been named Manager of the 516-bed Veterans Administration Research Hospital in Chicago.

Dr. Jan H. Tillisch, F.A.C.P., Rochester, Minn., has recently been made President-Elect of the Aero Medical Association at its convention in Washington, D. C.

Of interest to all Internists is the announcement of the American Hospital Association that the National Intern Matching Program has the task of matching 6,379 interns into the hospitals they want and vice versa. To complicate matters further is the fact that there are 11,075 internships to be filled.

Elections to Membership in the American College of Physicians

At the Thirty-sixth Annual Session, held in Philadelphia, Pa., April 25–29, the following candidates were elected to membership in the College (Fellows indicated in FULL CAPITALS; Associates, Lower Case):

ALBERT ABRAHAM ..... Morristown, N. J.
Frank Abrams ..... Pittsburgh, Pa.
John Denise Abrums ..... Albuquerque, N. M.
Samuel Dudleston Allison ..... Honolulu, T. H.
William Mims Allums ..... Shreveport, La.
JOHN BELLOWS ALSEVER ..... Bethesda, Md. (U.S.P.H.S.)
WILLIAM LEWIS ALSOBROOK ..... Nashville, Tenn. (V.A.)
NORMAN LaRUE ANDERSON ..... Asheville, N. C.
Robert Spencer Anderson ..... Nashville, Tenn.
Robert Hallett Areson ..... Upper Montclair, N. J.
WILLIAM JAMES ATKINSON, JR. ..... Mobile, Ala.
Joseph Howland Auchincloss, Jr. ..... Syracuse, N. Y.

JOSE BÁEZ-VILLASEÑOR ..... Mexico, D. F.
Victor Gerardo Balboni ..... Boston, Mass.
Donald Weesner Bales ..... Kingsport, Tenn.
HARRY EDGAR BANGHART ..... Philadelphia, Pa.
D(urtad) Richard Baronian ..... Providence, R. I.
Thomas Melvin Batchelor ..... Detroit, Mich.
Henry Douglas Beale ..... Toledo, Ohio
Charles Rische Beeson ..... Albuquerque, N. M.
Roy Herbert Behnke ..... Indianapolis, Ind.
Henry Stanley Bennett ..... Detroit, Mich.
Louis Berlin ..... Mount Vernon, N. Y.
Keehn W. Berry, Jr. ..... Birmingham, Ala.
Stephen Joseph Berte ..... M.C., U. S. Army
Carlos Enrique Bertran ..... San Juan, P. R.
ANTHONY ANDREW BIANCO ..... New York, N. Y.
Monte Leroy Binder ..... Newport News, Va.
JOHN HARDESTY BLAND ..... Burlington, Vt.
Ancel Usher Blaustein ..... New York, N. Y.
Charles Douglass Bonner ..... Boston, Mass.
Robert Orville Brandenburg ..... Rochester, Minn.
GEORGE JOSEPH BREBIS ..... Chicago, Ill.
Warren Daniel Brill ..... Washington, D. C.
THEODORE TOBIAS BRONK ..... Buffalo, N. Y. (V.A.)
ROBERT ARTHUR BRUCE ..... Seattle, Wash.
JAMES ARNOLD BRUSSEL ..... Queens Village, N. Y.
Abraham Solomon Buchberg ..... New York, N. Y.
William Horace Bullock ..... Washington, D. C.
PAUL AXTELL BUNN ..... Syracuse, N. Y.
SAMUEL SIMON BURDEN ..... Elkins Park, Pa.
WILLIAM CHAMPLIN BURRAGE ..... Portland, Maine
Susan Butler ..... Quincy, Mass.

NATHANIEL OGLESBY CALLOWAY ..... Chicago, Ill.
Anthony Paul Caputi ..... Newport, R. I.
Willard Cardwell ..... Greensboro, N. C.
Philip David Carmel ..... Brooklyn, N. Y.

WILFRED CARROL .....Newark, N. J.
Curtis Harold Carter .....Augusta, Ga.
Banks Raleigh Cates, Jr. .....Charlotte, N. C.
WILLIAM FRANK CERNOCK .....Chicago, Ill.
†Thomas Clark Chalmers .....Cambridge, Mass.
William Phalen Chapman .....Boston, Mass.
David Sanford Citron .....Charlotte, N. C.
Warren Evart Coggeshall .....Indianapolis, Ind.
Eli Bertram Cohen .....Los Angeles, Calif.
Robert Slonim Cohen .....Birmingham, Ala.
HAROLD COHN .....Brooklyn, N. Y.
John Martin Coleman .....Chicago, Ill.
Francis Leo Colpoys, Jr. .....Brookline, Mass.
Victor Galbraith Colvin .....M.C., U. S. Navy
Norman Donat Comeau .....Mt. Rainier, Md.
HERBERT WILLIAM COONE .....M.C., U. S. Air Force
ARTHUR CURTIS CORCORAN .....Cleveland, Ohio
Peter James Corrigan .....Cleveland, Ohio
FREDERIC EUGENE COWDEN .....Nashville, Tenn.
Kenneth Raymond Crispell .....Charlottesville, Va.
Gerald Edwin Cronk .....Tulsa, Okla.
David Lloyd Crowell .....New York, N. Y.
GEORGE MANNING CUMMINS, JR. .....Chicago, Ill.
Richard Bruce Cuthbert, Jr. .....Canastota, N. Y.
PAUL CUTLER .....Atlantic City, N. J.
SEYMOUR SAUL CUTLER .....Brooklyn, N. Y.

William Purdie Daines .....Ogden, Utah
Herbert Arthur Dann .....New York, N. Y.
Sidney Dann .....Brooklyn, N. Y.
Jean Flatt Davey .....Toronto, Ont., Can.
Jay Howard Davidson .....Philadelphia, Pa.
WILLIAM ANTHONY DAVIS .....Glen Ridge, N. J.
NORMAN VICTOR De NOSAQUO .....Chicago, Ill.
Robert Lovett Dewees .....Wilmington, Del.
EDMUNDS GREY DIMOND .....Kansas City, Kans.
John Jacob Dobkins .....Canton, Ohio
Francis Edmund Donoghue .....Rochester, Minn.
DAVID THOMAS DRESDALE .....Brooklyn, N. Y.
Leroy Edward Duncan, Jr. .....Rockville, Md. (U.S.P.H.S.)
Harvey Joseph Dworken .....Cleveland, Ohio
Richard Warren Dyke .....Indianapolis, Ind.

DAVID PRINCE EARLE, JR. .....Chicago, Ill.
John James Eckberg .....Erie, Pa.
‡RICHARD DALE ECKHARDT .....Iowa City, Iowa
Sherman Louis Egan .....South Bend, Ind.
HARRY JAY EPSTEIN .....Philadelphia, Pa.

CHESTER WILSON FAIRLIE, JR. .....Hartford, Conn.
STEFAN STANISLAUS FAJANS .....Ann Arbor, Mich.
Arthur Warren Feinberg .....Great Neck, N. Y.

† (M.C.) AUS.
‡ (M.C.) USNR.

DAVID FELDMAN ..... St. Louis, Mo.
John Francis Finnegan ..... Washington, D. C.
Louis Fishman ..... Hightstown, N. J.
Douglas Lincoln Forde ..... Pacific Palisades, Calif.
Ludwig Mathias Frank ..... West Hartford, Conn.
Sidney Norman Franklin ..... Philadelphia, Pa.
MILTON HAROLD FREEDMAN ..... Atlanta, Ga.
HAROLD AARON FRIEDMAN ..... Rochester, N. Y.
Lester David Friedman ..... Yonkers, N. Y.

Norman Arthur Gale ..... San Diego, Calif.
GUILLERMO GARCIA-LOPEZ ..... Havana, Cuba
GEORGE E. GATES ..... South Bend, Ind.
JOSEPH EMIL GERACI ..... Rochester, Minn.
ISADORE EARLE GERBER ..... New York, N. Y.
ADOLPH JOSEPH GERL ..... New York, N. Y.
William Hayes Getty ..... Evansville, Ind.
Frederick Conrad Gevalt ..... Sharon, Conn.
Henry Monnier Gewin ..... Mobile, Ala.
FRANCISCO GÓMEZ MONT ..... Mexico, D. F.
Joseph Goodgold ..... New York, N. Y.
Raymond Dennis Goodman ..... Beverly Hills, Calif.
SANDER GOODMAN ..... Cincinnati, Ohio
Abraham Maury Gordon ..... Louisville, Ky.
ALVIN JOSEPH GORDON ..... New York, N. Y.
Gilbert Lee Gordon ..... Mount Kisco, N. Y.
NORMAN ERNEST GOULDER ..... Columbus, Ohio
Frank Whitton Govern ..... M.C., U. S. Army
James Dakers Carrie Gowans ..... Swampscott, Mass.
†WILLIAM JOSEPH GRACE ..... New York, N. Y.
Joseph Lewis Grant ..... White River Junction, Vt. (V.A.)
Kendall Decatur Gregory ..... Gulfport, Miss.
Harold William Grossman ..... Jersey City, N. J.
Harold Grubin ..... Newark, N. J.
ERIC ROBIN GUBBAY ..... Winnipeg, Man., Canada
John Kelly Guck ..... New York, N. Y.
Samuel Barry Guze ..... St. Louis, Mo.

THOMAS ARTHUR HAEDICKE ..... Jackson, Miss. (V.A.)
RICHARD DeWAYNE HAINES ..... Temple, Tex.
Leonard Norman Hallinger ..... New Rochelle, N. Y.
John Church Ham ..... Providence, R. I.
Longstreet Cavett Hamilton ..... M.C., U. S. Army
GEORGE WESLEY HAMMEL ..... El Dorado, Kans.
GEORGE JOHN HAMWI ..... Columbus, Ohio
David Gregory Hanlon ..... Rochester, Minn.
Frank Roger Hanrahan, Jr. ..... Cleveland, Ohio
†Edmund Barton Hardin ..... Santa Monica, Calif.
Francis Williams Hare ..... Madison, Ind.
Henry Fauntleroy Harris ..... Port Chester, N. Y.
HOWARD YEAGER HARRIS ..... Wilkes-Barre, Pa.
WILLIAM HENRY HARRIS, JR. ..... Richmond, Va.

† (M.C.) AUS.

THEODORE HENRY HARWOOD ..... Grand Forks, N. D.
SILAS BEACH HAYS ..... M.C., U. S. Army
Leon David Hellman ..... New York, N. Y.
Gordon Ross Hennigar, Jr. ..... Richmond, Va.
Walter Lester Henry, Jr. ..... Washington, D. C.
Isadore Herman ..... Passaic, N. J.
ROBERT SIMON HERZOG ..... Philadelphia, Pa.
Norman Peirce Hill ..... Fall River, Mass.
DON CARLOS HINES ..... Indianapolis, Ind.
Charles Kennedy Holland, Jr. ..... McAlester, Okla.
WILLIAM HOROWITZ ..... New York, N. Y.
Jay Carrol Hoyt ..... M.C., U. S. Army
Van William Hunt ..... Mason City, Iowa
Milton Mayer Hurwitz ..... St. Paul, Minn.

IRVING IMBER ..... Reading, Pa.

Dudley Pennington Jackson ..... Baltimore, Md.
Avrohm Jacobson ..... Asbury Park, N. J.
Belle Elizabeth Jacobson ..... New Rochelle, N. Y.
Martin Ernest Janssen ..... St. Paul, Minn.
Eugene Vance Jobe ..... M.C., U. S. Navy
Max Edward Johnson ..... New Orleans, La.
Robert Dale Johnson ..... Ann Arbor, Mich.
Stephen Noland Jones ..... Rockville, Md.

#Abraham Kagan ..... Natick, Mass.
Alfred Julian Kaltman ..... New York, N. Y.
Harold Karlin ..... Boston, Mass.
Frank Louis Karp ..... Brooklyn, N. Y.
Israel Altman Karrel ..... St. John, N.B., Canada
WILLIAM HENRY KAUFMAN ..... Roanoke, Va.
B(enjamin) H(arrison) Kean ..... New York, N. Y.
Stephen Ridinger Keister ..... Erie, Pa.
Donald H. Keller ..... Washington, D. C.
Rita Marie Kelley ..... Boston, Mass.
Robert Orcutt Kellogg ..... Bangor, Maine
Donald Charles Kent ..... M.C., U. S. Navy
Donald Lawrence Kessler ..... Chicago, Ill.
Joyce Walter Kingsley, Jr. ..... Detroit, Mich.
Clayton Harold Klakeg ..... Rochester, Minn.
Martin Seler Kleckner, Jr. ..... Chicago, Ill.
CHARLES KLEIN ..... New York, N. Y.
HOWARD ALBERT KLEIN ..... Detroit, Mich.
CHARLES E. KLONTZ ..... Rockford, Ill.
William Bernard Knapp ..... Chicago, Ill.
Duval Holtzclaw Koonce ..... M.C., U. S. Air Force
DAVID KRAPIN ..... New Rochelle, N. Y.
HOWARD USHER KREMER ..... Philadelphia, Pa.
SIDNEY IRVING KREPS ..... New York, N. Y.
SAM KRUGER ..... Highland Park, Ill.
Lawrence Sydney Kryle ..... New York, N. Y.

#USPHS (R)

Robert Lee Lam ..... St. Louis, Mo.
†Donald Giltner Landale ..... San Diego, Calif.
Robert Everett Lane ..... Tacoma, Wash.
Edward Langdon ..... Omaha, Nebr.
Jules Hilbert Last ..... Highland Park, Ill.
Robert Oscar Levitt ..... Chicago, Ill.
ALYS HARRIS LIPSCOMB ..... Memphis, Tenn.
Armand Littman ..... Chicago, Ill.
ALLEN WINCH LOCKE ..... Wellesley Hills, Mass.
Alfonso Anthony Lombardi ..... New York, N. Y.
John Francis Loughlin ..... Augusta, Maine (V.A.)
Edwin Forrest Lovering ..... Pawtucket, R. I.
Joseph Lozner ..... Augusta, Ga. (V.A.)
Norton M. Luger ..... Fresh Meadows, N. Y.
Edgar Frank Luton ..... Memphis, Tenn. (V.A.)

Warren Lowell Macaulay ..... Fargo, N. D.
HAROLD HAZE MACUMBER ..... Chickasha, Okla.
Stephen Charles F. Mahady ..... Utica, N. Y.
Robert Allen Mandelbaum ..... Brooklyn, N. Y.
Harold Marcus ..... Brooklyn, N. Y.
HAROLD MARGULIES ..... Des Moines, Iowa
Harold Irving Mark ..... Penns Grove, N. J.
Herbert Mark ..... White Plains, N. Y.
HUGH MATHIS MASON ..... Beverly Hills, Calif.
FRANK PELLETREAU MATHEWS ..... Olympia, Wash.
Kenneth Pine Mathews ..... Ann Arbor, Mich.
William Frank Mazzitello ..... St. Paul, Minn.
Archie McCallister, Jr. ..... Miami, Fla.
Malcolm Christian McCord ..... Denver, Colo.
JAMES EDWARD McCORMACK ..... New York, N. Y.
John Marshall McCoy ..... M.C., U. S. Army
Wallace Gilfillan McCune ..... Philadelphia, Pa.
MARCUS DENNEY McDIVITT ..... Pittsburgh, Pa.
Howard McEwen ..... Calgary, Alta., Canada
†CHARLES JOSEPH McGEE ..... Brockton, Mass.
James Joseph McGinnis ..... San Francisco, Calif.
BERNARD FRANCIS McLAUGHLIN ..... Burlingame, Calif.
Elmore Rice McNeal ..... Youngstown, Ohio
Albert Louis McQuown ..... Baton Rouge, La.
Burtis Jackson Mears ..... St. Paul, Minn.
Theo Howell Mees ..... Lumberton, N. C.
WILLIAM MENIN ..... Philadelphia, Pa.
FERNANDO MILANES ..... Havana, Cuba
Joseph Morton Miller ..... Boston, Mass.
Walter Rutledge Miller ..... Johnson City, Tenn.
William Robert Milnor ..... Baltimore, Md.
§Eduardo Mirabal-Font ..... San Juan, P. R.
Alfred Adam Mitchell ..... Elmira, N. Y.
SIDNEY PEARCE MITCHELL ..... Palo Alto, Calif.
Benjamin Andrin Moeller, Jr. ..... Memphis, Tenn. (V.A.)
HERBERT CHARLES MOFFITT, JR. ..... San Francisco, Calif.

† (M.C.) AUS.
§ (M.C.) USAFR.

Benjamin Franklin Montague, Jr. .....Montgomery, Ala. (V.A.)
Robert Rice Montgomery .....Washington, D. C.
Eduardo Montilla .....San Juan, P. R.
FRANK HAMPTON MOORE .....Bowling Green, Ky.
James Francis Morrell .....M.C., U. S. Navy
Hascall Henry Muntz .....Tyler, Tex.
Roland Virgil Murphy .....Tucson, Ariz.
Warren Powers Laird Myers .....New York, N. Y.
JAMES GIFFORD MYHRE .....Minneapolis, Minn.

Morris Newberg .....Queens Village, N. Y.
WALTER NEWMAN .....Bronx, N. Y. (V.A.)
Joseph Tatnall Lea Nicholson .....Devon, Pa.

WILLIAM ARTHUR OILLE .....Toronto, Ont., Canada
Felix Albert Olash .....Louisville, Ky.
Wesley Marion Oler .....Washington, D. C.
EDWIN SAMUEL OLSAN .....Rochester, N. Y.
Charles William Ordman .....Washington, D. C.
Donald Charles Overy .....Ann Arbor, Mich.

Thomas Fite Paine, Jr. .....Birmingham, Ala.
Delmo August Paris .....Detroit, Mich.
ALFRED EDWARD PASSERA .....Woodside, N. Y.
BERNARD HENRY PASTOR .....Philadelphia, Pa. (V.A.)
Ralph Francis Patten .....Silver Spring, Md.
Beverly Carodine Payne .....Ann Arbor, Mich.
CARLYLE ALLEN PAYNE .....Grand Rapids, Mich.
Edward Schmidt Petersen .....Chicago, Ill.
SAMUEL PHILLIPS .....Memphis, Tenn. (V.A.)
Leslie Staebler Pierce .....Greensburg, Pa.
Forrest Williford Pitts .....M.C., U. S. Army
CHARLES POKORNY .....Halstead, Kans.
Edward Bernard Polin .....Philadelphia, Pa.
Harold Zvy Pomerantz .....Montreal, Que., Canada
William Wainwright Houston Pote, Jr. .....Loma Linda, Calif.
Luigi Alberto Principato .....Camden, N. J.
WALTER HERBERT PRITCHARD .....Cleveland, Ohio
Newton George Pritchett .....Raleigh, N. C.
George Prussin .....Brooklyn, N. Y.
Raoul Constantine Psaki .....M.C., U. S. Army

Ione Eleanor Railton .....San Francisco, Calif.
ELI ALBERTO RAMIREZ-RODRIGUEZ ...Rio Piedras, P. R. (V.A.)
Eugene John Ranke .....Chicago, Ill.
Samuel I. Rapaport .....Long Beach, Calif. (V.A.)
Mortimer Raphael .....Monroe, La.
CHARLES EDWARD RATH .....Washington, D. C.
WILLIAM HENRY REIFF .....Oklahoma City, Okla.
Henry Renfert, Jr. .....Austin, Tex.
Charles Ressler .....New York, N. Y.
‡George Johnson Rhodes .....Pittsburgh, Pa.
ISAAC HYMAN RICHTER .....Brooklyn, N. Y.

‡ (M.C.) USNR.

George Alfred Rie ..... Flushing, N. Y.
Norman Righthand ..... Stamford, Conn.
Roger William Robinson ..... Worcester, Mass.
Melvin Herbert Rodman ..... West Haven, Conn. (V.A.)
MANUEL RODSTEIN ..... New York, N. Y.
ARTHUR ERNEST THÉODORE ROGERS . Keene, Calif.
Andries Isaac Roodenburg ..... Rochester, N. Y.
Isadore Rose ..... Philadelphia, Pa.
Charles Rosen ..... Chatham, N. Y.
EDGAR ROSEN ..... Oakland, Calif.
BENJAMIN ROSENBERG ..... Brooklyn, N. Y.
Julius Rosenberg ..... Brooklyn, N. Y.
William Harold Rosenblatt ..... Jackson, Miss.
SAMUEL ROSENTHAL ..... Milwaukee, Wis.
HAROLD PHILMORE ROTH ..... Cleveland, Ohio (V.A.)
Robert Thomas Rowland ..... San Diego, Calif.

Stuart Arnold Safdi ..... Cincinnati, Ohio
MELVIN RAYMOND SALK ..... Chicago, Ill.
MAX SAMTER ..... Oak Park, Ill.
SALVATORE MARIO SANCETTA ..... Cleveland, Ohio
Samuel Saslaw ..... Columbus, Ohio
John Sutphin Schechter ..... Indianapolis, Ind.
William Arnold Schiess ..... Syracuse, N. Y.
James Ferdinand Schieve ..... Columbus, Ohio
Charles Schnall ..... Philadelphia, Pa.
Frederick Andrew Schroeder ..... Sacramento, Calif.
Norman McLean Scott, Jr. ..... M.C., U. S. Army
Charles Herbert Sears ..... Santa Ana, Calif.
Albert Segaloff ..... New Orleans, La.
Arthur Selzer ..... San Francisco, Calif.
ISADORE CHARLES SHARON ..... Cincinnati, Ohio
HARMAN ALBERT SHECKET ..... Cleveland, Ohio
ARCHIBALD DANIEL SHEERAN ..... Princeton, N. J.
Winston Kinney Shorey ..... Philadelphia, Pa.
Donald Shotton ..... Lynchburg, Va.
Murray William Shulman ..... Newark, N. J.
Reginald Hughes Smart ..... Los Angeles, Calif.
ALFRED LITTLEFIELD SMITH ..... Richmond, Va.
Clarence Albert Smith ..... Washington, D. C. (U.S.P.H.S.)
DeWitt Hendee Smith ..... Princeton, N. J.
George Paul Smith ..... Grand Junction, Colo.
William Philip Smith ..... Coral Gables, Fla.
WILLIAM WEBER SMITH ..... Beverly Hills, Calif.
Sidney Seymour Sobin ..... Beverly Hills, Calif.
William Boyer Soltz ..... New York, N. Y.
†Alvin Somberg ..... Omaha, Nebr. (V.A.)
Robert Monroe Soule ..... Melrose, Mass.
Samuel David Spatt ..... Brooklyn, N. Y.
William George Speed, III ..... Baltimore, Md.
§FRANCIS MILTON SPENCER ..... San Angelo, Tex.
DAVID STEINBERG ..... Jamaica, N. Y.

† (M.C.) AUS.
§ (M.C.) USAFR.

CHARLES A(RTHUR) L(LOYD) STEPHENS, JR. ..... Tucson, Ariz.
EDWARD AMBERG STERN ..... Rochester, N. Y.
HERMAN HULL STONE ..... Riverside, Calif.
Emery Kaufmann Stoner ..... Philadelphia, Pa.
Willard Cyrus Stoner, Jr. ..... Cleveland, Ohio
John Edgar Strang ..... Philadelphia, Pa.
IRVIN SUSSMAN ..... Bridgeton, N. J.
Jean Margaret Swain ..... Agnew, Calif.
‡JEROME MARVIN SWARTS ..... Memphis, Tenn. (V.A.)
SAMUEL LEWIS SWILLER ..... Brooklyn, N. Y.
JOHN LOUIS SWITZER ..... Chicago, Ill.

Burton Samuel Tabakin ..... Burlington, Vt.
John Stephen Thompson ..... Morristown, N. J.
Jose Manuel Torres-Gomez ..... San Juan, P. R.
ROBERT BRUCE TUDOR ..... Bismarck, N. D.
Theodore Turnbull ..... Tulsa, Okla.
Richard Current Turrell ..... Louisville, Ky.

Herman H. Ulevitch ..... Dallas, Tex.
Alvin Lamkay Ureles ..... Rochester, N. Y.

TEODOSIO VALLEDOR ..... Havana, Cuba
Ray Alfred Van Ommen ..... Cleveland, Ohio
ALFRED VOGL ..... New York, N. Y.
Louis Jack Vorhaus, II ..... New York, N. Y.

Philip Lawrence Wainman ..... Los Angeles, Calif.
Maurice Harold Wald ..... Winnetka, Ill.
Alvie Carl Walker ..... Waynesburg, Pa.
§Stanley Lawrence Wallace ..... Brooklyn, N. Y.
George Charles Walsh ..... Vancouver, B. C., Canada
Frank Pelouze Ward ..... Lumberton, N. C.

‡ (M.C.) USNR.
§ (M.C.) USAFR.

OBITUARIES

DR. PAUL BRINDLEY

Dr. Paul Brindley, F.A.C.P., of Galveston, Tex., died Dec. 28, 1954, of a myocardial infarction.

A native of Texas, Dr. Brindley was born in Maypearl, Dec. 27, 1896. He graduated from the University of Texas in 1923 with the degree of Bachelor of Science and received his M.D. degree from the same University in 1925. Upon graduation he became an Instructor in the Department of Pathology of the University of Texas School of Medicine and rose through the various grades to become Professor of Pathology in 1929, which position he occupied until the time of his death. He had served as Head of the Department of Pathology and as Pathologist-in-Chief to the hospitals of the Medical Branch of the University of Texas for 25 years.

He was also Consulting Pathologist for the United States Public Health Service Hospital, Galveston, 1931–54. He served in the same capacity in the University of Texas M. D. Anderson Hospital for Cancer Research, Houston, and the Lackland Air Force Base Hospital, San Antonio.

A gifted teacher, he was lucid, enthusiastic and planned carefully with the best interests of his students in mind. He considered teaching to be his first and most important duty. He contributed liberally to pathological literature and made enduring contributions to the subjects of aneurysm, Madura foot, and malignant disease.

Dr. Brindley was a member of the Galveston County Medical Society and the Texas and American Medical Associations. He had served as President of his county society in 1949 and had been Chairman of the Section on Clinical Pathology in the Texas Medical Association in 1942. He was President of the Texas Society of Pathologists in 1946. In addition, Dr. Brindley was a member of the American Association of Pathologists and Bacteriologists, the Society of Tropical Medicine, the International Society of Geographic Pathologists, the International Association of Medical Museums, and the American Association for the Advancement of Science. He was a Fellow of the American Society of Clinical Pathologists and of the American College of Pathologists. He had been a Fellow of the American College of Physicians since 1936 and was a Diplomate of the American Board of Pathology. He was a founder of the Galveston County Unit of the American Cancer Society and maintained an interest in this organization throughout his life.

In recognition of his contributions to pathology, Dr. Brindley had been selected to receive the first Caldwell Memorial Award of the Texas Society of Pathologists. The scroll and gold medal were presented to Mrs. Brindley after his death. His interests other than medicine were music, history, biography, and photography. He was a skilled amateur photographer.

The following quotation from a memorial tribute read at the faculty meeting of the University of Texas School of Medicine, Feb. 1, 1955, reveals the esteem in which he was held by his colleagues: "No institution of merit can endure without men like Doctor Paul Brindley. Progress and happiness are impossible without them. Men whose superior endowments and motives make them humble before God, modest in recognition of the minute fragment that can be any one person's share in the achievements of the race, understanding and kindly towards the needs of others, honest and brave in meeting their own. Such men face life with the determination to leave it

a little better than they found it, and they pursue this course unswervingly to the end. In Paul Brindley we have been privileged to know and associate with a noble member of mankind."

D. W. Carter, Jr., M.D., F.A.C.P.,
Governor for Texas

DR. RAYMOND CLARK

Dr. Raymond Clark, F.A.C.P., was born in 1870, and died in the Johns Hopkins Hospital, Baltimore, on Jan. 23, 1955, of carcinoma of the pancreas.

Dr. Clark was graduated from the Columbia University College of Physicians and Surgeons in 1895. He was former Consultant in Medicine at the Brooklyn and Beth-El Hospitals, and former Chief of Medicine and Consultant in Medicine at the Brownsville and East New York Hospitals. Virtually a charter member of the American College of Physicians, Dr. Clark was elected a Fellow in 1916.

His friends and confreres note with deep regret Dr. Clark's death.

Irving S. Wright, M.D., F.A.C.P.,
Governor for Eastern New York

DR. EVARTS V. DEPEW

Dr. Evarts Vaine DePew, F.A.C.P., of San Antonio, Tex., died of uremia on Feb. 7, 1955, at the Brooke Army Hospital in San Antonio. He had practiced medicine in San Antonio for 48 years, specializing in gastroenterology.

Dr. DePew was born on Jan. 2, 1876, at Wolf Lake, Ind. He received an A.B. degree from Hillsdale College in 1900, a B.S. degree from the University of Chicago in 1901, and graduated in medicine in 1904 from Rush Medical College. In preparation for his practice of gastroenterology, Dr. DePew did special work under the late Dr. H. I. Sippy of Chicago, and in Berlin, Germany.

During World War I he was a Major in the Medical Corps of the United States Army and served in Georgia and Kentucky.

He was President of the Bexar County Medical Society in 1921 and a Director of the same society in 1945. He was a Charter Member of the Texas Rheumatism Association and also held memberships in the Texas, Southern, and American Medical Associations and the International Medical Assembly of Southwest Texas. He was elected a Fellow of the American College of Physicians in 1928.

Dr. DePew had served organized medicine in many different ways. He was a member and former Secretary of the Fifth District Medical Society; he had been Secretary of the Section on Medicine and Diseases of Children of the Texas Medical Association in 1916 and 1921, and of the Section on Public Health in 1932.

He was elected an Honorary Member of the Texas Medical Association in 1953, following his retirement from active practice the preceding year.

Long an outstanding member of the medical profession of Texas, Dr. DePew was held in high esteem by his colleagues, his friends and his patients.

D. W. Carter, Jr., M.D., F.A.C.P.,
Governor for Texas

DR. EDGAR DURBIN

Dr. Edgar Durbin, F.A.C.P., of Denver, Colo., died suddenly and entirely unexpectedly on Monday morning, March 21, 1955, presumably of an acute coronary occlusion. He was born in Denver, May 14, 1903, graduated from the Harvard Medical School, and practiced medicine in Denver the remainder of his life, with the exception of four years with the armed forces during World War II.

Early in his successful professional career, Dr. Durbin began to specialize in cardiology. In more recent years he became consultant in this field to most of the hospitals of Denver, as well as to the Veterans Administration Hospitals in Denver, Cheyenne and St. Louis. He was active in the affairs of the Colorado Heart Association and was its President from 1949 to 1952; and, in fact, one of his executive associates said, "He had shaped the policy of the organization ever since."

Dr. Durbin had been President of the Denver Medical Society and was an active member of the Colorado State Medical Society and the American Medical Association. He was a Diplomate of the American Board of Internal Medicine and had been a Fellow of the American College of Physicians since 1937.

Dr. Durbin was blessed by possessing an engaging personality, an excellent and well-disciplined mind, and a true spirit of professional service.

C. F. KEMPER, M.D., F.A.C.P.,
Governor for Colorado

DR. HERBERT E. FLEWELLING

Born in Watertown, Mass., on June 6, 1914, Dr. Herbert Eldridge Flewelling (Associate), died at his home in Peterborough, N. H., on Nov. 13, 1954, at the age of only 40 years. He was graduated from Belmont, Mass., High School in 1933, from Harvard College in 1937, from Tufts College Medical School in 1941, and interned at the Methodist Hospital in Brooklyn, N. Y. He served in the Medical Department of the Army Air Corps from 1942 to 1945 in North Africa and Italy. Following the war he returned to the Methodist Hospital, going from there to the Veterans Hospital in Framingham, Mass., before taking up his practice in New Hampshire.

He was a member of his county and state societies and of the American Medical Association; he became an Associate of the American College of Physicians in 1950. He was certified by the American Board of Internal Medicine in 1951.

Dr. Flewelling enjoyed his home and family to an unusual extent and did many things together with them as a family group. He greatly enjoyed amateur carpentry, had a work shop in his cellar and did much of the work on his own house. He enjoyed the outdoors, had a garden and had planned over the years to improve a large acreage of cleared land.

He had an unusual number of real friends, and one of his outstanding characteristics was his very genuine kindliness, courtesy, consideration of others and a deep sense of curiosity and thoroughness in whatever he undertook. He was respected and held in great admiration by his patients. Professionally he maintained a very high standard and did much to improve and maintain a high standard of medical practice in his community.

He was a man of admirable qualities. Optimism and enthusiasm characterized him, and the vigorous and cheerful way with which he undertook every task was contagious and heartening to all concerned. He thrived on responsibility and was

satisfied only with the fullest perfection within his power. His humor was quick and quiet and clean, and he knew no bitterness. Dr. Flewelling excelled as a family man, as a physician and as a friend. The community and the College have lost an extremely valuable member.

SVEN M. GUNDERSEN, M.D., F.A.C.P.,
Governor for New Hampshire

DR. HARRY FREUND

Dr. Harry Freund (Associate) was born in New York City on Aug. 7, 1905. He died in the Montefiore Hospital on Jan. 9, 1955, from rheumatic heart disease and chronic pancreatitis.

He received the degree of Bachelor of Arts from Columbia University in 1925 and the degree of Doctor of Medicine from Columbia University College of Physicians and Surgeons in 1929. Dr. Freund interned at the Brooklyn Jewish Hospital, 1929–31, and had been Assistant Physician to the Diabetes Outpatient Department since 1932. He served as Assistant Visiting Physician at the Cumberland Hospital, 1936–46, as Assistant Electrocardiographer in the Cardiac Outpatient Department, 1937–43, as Associate Visiting Physician, 1946–50, and as Attending Physician, 1950–55.

Dr. Freund was a member of the Kings County Medical Society, the Medical Society of the State of New York, the American Medical Association, the Clinical Society of the New York Diabetes Association, the American Diabetes Association, and Alpha Omega Alpha fraternity. He was a Diplomate of the American Board of Internal Medicine and became an Associate of the American College of Physicians in 1950.

It is with deep regret that we record the passing of Dr. Freund.

IRVING S. WRIGHT, M.D., F.A.C.P.,
Governor for Eastern New York

DR. CHARLES M. GRIFFITH

Dr. Charles Marion Griffith, F.A.C.P., who had a long career in governmental medical service, died Dec. 19, 1954, in the Veterans Administration Hospital, Washington, D. C.

Dr. Griffith was born in Jasper, Tenn., on May 22, 1882. He received his M.D. degree from the University of Tennessee College of Medicine in 1908 and completed his internship in the City Hospital, Nashville, in 1909. After several years of association with his father, he engaged in private practice in Tullahoma, Tenn., from 1912 to 1916. He served in World War I as Surgeon, 109th Infantry Regiment, 28th Division, from 1917 until 1919, when he was discharged with the rank of Major.

Dr. Griffith was then commissioned in the United States Public Health Service (at that time charged with the medical care of veterans). His first assignment was as Chief of the Surgical Service at the hospital in Alexandria, La., 1919–23; this was followed by a year of duty in charge of the Veterans Hospital in Tuskegee, Ala. He transferred to the Veterans Bureau upon its formation in 1924 and was assigned to the Central Office, Washington, D. C. He continued on duty with the Veterans Administration when it was organized in 1930.

Dr. Griffith served successively as Chief of the Surgical Service and Executive Officer in the Central Office until his appointment as Medical Director of the Veterans Administration in September, 1930. He continued in this capacity until November,

1945, when he was assigned as Manager to the Veterans Administration Hospital, Washington, D. C. Upon his retirement on Dec. 31, 1951, he continued to make his home in Washington. Dr. Griffith was a Fellow of the American College of Surgeons, a member of the Association of Military Surgeons of the United States (President, 1935–36), and had been a Fellow of the American College of Physicians since 1931.

For a period of almost 35 years, Dr. Griffith's career was devoted to the medical care of soldiers and veterans of the Nation. He was an able administrator and served the citizens of our country with great loyalty and efficiency.

WILLIAM S. MIDDLETON, M.D., M.A.C.P.,
Chief Medical Director,
Governor for the Veterans Administration

DR. SAMUEL GOLDBERG

Dr. Samuel Goldberg, M.D., F.A.C.P., of Philadelphia, died Nov. 26, 1954, of myocardial infarction.

Born in New York City, June 12, 1889, he received his M.D. degree from the Medico-Chirurgical College of Philadelphia in 1912. Dr. Goldberg was appointed to the faculty of Temple University School of Medicine in 1923 as a Lecturer in Pediatrics, and at the time of his death had been Clinical Professor of Pediatrics since 1931. He was Consulting Pediatrician at the Jewish Hospital, where he had been a member of the staff since 1913, and was also former Pediatrician at the Clinic of the Philadelphia Skin and Cancer Hospital, Willow Crest for Convalescents, Willow Grove, and Consultant Pediatrician, Riverview Hospital, Norristown. Dr. Goldberg was forced to retire from private practice in 1948 because of arthritis.

A Fellow of the American Academy of Pediatrics, he was a former President of the Philadelphia Pediatric Society and was a member of the Philadelphia Medical Club, Philadelphia County Medical Society, Medical Society of the State of Pennsylvania, American Medical Association, the American Association for Pediatric Teaching and Phi Delta Epsilon fraternity. Dr. Goldberg became a Fellow of the American College of Physicians in 1933.

DR. CORNELIUS A. O'LEARY

Dr. Cornelius Arthur O'Leary, F.A.C.P., died on Jan. 13, 1955, in Tucson, Ariz., of carcinoma of the gallbladder with metastases to the liver.

Born in Brooklyn, N. Y., May 8, 1884, Dr. O'Leary spent most of his active medical life in the New York City area. After receiving his medical degree at Long Island College Hospital in 1908, he pursued postgraduate studies in Edinburgh and Vienna before taking his internship and residency at the Brooklyn and New York Foundling Hospitals. In 1918 he was appointed Associate Superintendent of the Suffolk Sanatorium, Holtsville, N. Y., and served there many years as a member of its Board of Managers. During World War I, he was Medical Examiner for the Draft Board, Cardiac and Pulmonary Division, at Bay Shore, Long Island, N. Y. He was formerly a member of the staffs at St. Charles Orthopedic Clinic, Brooklyn; St. Charles and John T. Mather Memorial Hospitals, Port Jefferson; Southside Hospital, Bay Shore; and Belle Alto and Patchogue Hospitals, Patchogue.

In 1932 Dr. O'Leary was forced to retire because of chronic asthma with bronchiectasis and moved to Arizona, where he lived in Phoenix before removing

to Tucson. A former member of the Suffolk (N. Y.) County Medical Society, the Medical Society of the State of New York, the American Medical and National Tuberculosis Associations, Dr. O'Leary was also a member of Alpha Kappa Kappa Medical Fraternity and had been a Fellow of the American College of Physicians since 1929.

LESLIE R. KOBER, M.D., F.A.C.P.,
Governor for Arizona

DR. FLOYD L. ROGERS

Floyd Leslie Rogers, M.D., F.A.C.P., of Lincoln, Nebr., was born in Le Mars, Iowa, on Aug. 27, 1896, and died Nov. 30, 1954.

Dr. Rogers received his Bachelor of Science degree from the University of Nebraska in 1919 and the degree of Doctor of Medicine in 1922 from Northwestern University Medical School. Following graduation from medical school, Dr. Rogers was for a short time in the obstetrical service at the Chicago Lying-In Hospital before taking a residency in medicine in Michael Reese Hospital.

Upon completion of his residency, Dr. Rogers launched his career in the practice of medicine, limited to internal medicine, in Lincoln, Nebr. At the time of his death, he was Attending Physician at the Lincoln General and Bryan Memorial Hospitals. Formerly he had been Attending Physician at St. Elizabeth Hospital, Chief of the Medical Service at Bryan Memorial Hospital, Consulting Physician and Pathologist at the U. S. Veterans Hospital and Lecturer at the University of Nebraska Dental College.

Dr. Rogers was especially interested in diabetes and did a great deal of research and study on this disease. He served as President and Vice President of the West Central Diabetes Association. He did a magnificent job in publicizing diabetes and thereby helped to make the people of his state diabetes-conscious. He furthermore demonstrated his interests in diabetes by founding the Springdale Camp for Diabetic Children, which is to be renamed, in his memory, The Doctor Floyd Rogers Camp for Diabetic Children.

Dr. Rogers was an untiring worker on committees of the Nebraska State Medical Association and the Lancaster County Medical Society, and was a former President of each as well as of the North Central Medical Conference. He was a member of the American Medical Association and the American Diabetes Association and was a Diplomate of the American Board of Internal Medicine. He had been a Fellow of the American College of Physicians since 1934.

Dr. Rogers was beloved by his colleagues, not only because of his interests in his chosen specialty but also because of his activities in the realms of forensic medicine. He was a member highly worthy of Fellowship in the College, participating in regional programs and attending the majority of annual and regional meetings of the College. His unselfish and untiring efforts in the behalf of the better practice of medicine will be remembered always, and his presence will be missed from the many offices, councils and committees on which he served.

To his bereaved family, Mrs. Helen Rogers and daughters, Mrs. Caroline Mills and Miss Ann Rogers, the Nebraska Fellows and Associates of the American College of Physicians extend their sincere condolences.

JOSEPH D. MCCARTHY, M.D., F.A.C.P.,
Governor for Nebraska

DR. LOWELL S. SELLING

Lowell Sinn Selling, M.D., Ph.D., F.A.C.P., died suddenly of a heart attack on Jan. 18, 1955, following surgery for a fractured hip, at the Orange Memorial Hospital, Orlando, Fla.

Dr. Selling was born March 17, 1902, in Detroit, Mich. He received his medical degree at University and Bellevue Hospital Medical College in 1928, his Ph.D. at Columbia University in 1930, and his D.P.H. at the University of Michigan in 1939. He held many teaching posts at various colleges and universities and for many years was Director of the Psychopathic Clinic of the Recorder's Court of the City of Detroit. He was a Diplomate of the National Board of Medical Examiners and of the American Board of Psychiatry and Neurology. He was the author of various publications concerning neuropsychiatry and held offices in numerous national professional societies. He had been a Fellow of the American College of Physicians since 1938.

In 1947, for reasons of health, Dr. Selling moved to Florida, where he assumed the post of Director of the Mental Health Program in the State Board of Health. In 1948 he moved to Orlando, where he established a private practice of psychiatry and assumed Directorship of the Orange County Health Department Guidance Clinic and of the Polk County Guidance Center at Bartow. In the ensuing years he maintained a large private practice and produced many contributions to the psychiatric literature.

Dr. Selling is survived by his wife, Mary Paradis Selling, a son and a daughter.

WILLIAM C. BLAKE, M.D., F.A.C.P.,
Governor for Florida

DR. JAMES W. SHERRILL

Dr. James Winn Sherrill, F.A.C.P., of La Jolla, Calif., died of heart disease Jan. 4, 1955.

Dr. Sherrill was born in Temple, Tex., April 22, 1890, and was graduated from Baylor University in 1913. He received his M.D. degree from the Johns Hopkins University School of Medicine in 1917 and served as a Lieutenant in the Medical Corps of the U. S. Army during World War I from 1918 through 1919. He had a rich experience in tropical diseases during an internship at the Gorgas Memorial Hospital in Panama.

Dr. Sherrill became associated with Dr. Frederick M. Allen in the study of diabetes in New York City and Morristown, N. J. Diabetes became his lifelong interest and he became the first and only Director of the newly created Scripps Metabolic Clinic-Hospital at La Jolla in 1924. Under his direction this clinic has enjoyed a sound growth since its inception and he guided an extensive remodeling one year ago. He had been a Lecturer in Medicine, University of California Medical School since 1927 and a Consultant in Metabolic Diseases, U. S. Naval Hospital, San Diego, since 1946. He was the author of numerous papers on metabolic diseases, a Diplomate of the American Board of Internal Medicine, and a member of the San Diego County Medical Society, California and American Medical Associations, Association for the Study of Internal Secretions, American Diabetes Association, and the California Society of Internal Medicine. He was elected to Fellowship in the American College of Physicians in 1929.

Dr. Sherrill combined, in a remarkable way, the qualities of an internist, specialist in diabetes, organizer and administrator with a keen financial insight which

permitted a new and untried institution to weather the vicissitudes of the depression and emerge in its present form. He will be missed by his many friends throughout the world.

ARTHUR A. MARLOW, M.D., F.A.C.P.

DR. MARY F. SWEET

Dr. Mary Frances Sweet, F.A.C.P., was born in Camillus, N. Y., Feb. 1, 1874. She died in Decatur, Ga., Nov. 19, 1954.

Dr. Sweet attended Syracuse University and was graduated from the College of Medicine in 1900. She then interned at the New England Hospital for Women and Children in 1901. Following this year of postgraduate training, she became an Assistant in Pediatrics at the Albany (N. Y.) Free Dispensary during 1902–03. For the next five years she was engaged in private practice in Syracuse, N. Y.

In 1908 Dr. Sweet became the college physician and Professor of Physical Education at Agnes Scott College in Decatur, a post she held until her retirement in 1937. In addition to caring for the health of the students, Dr. Sweet directed her untiring activity to the newly formed Department of Physical Education and to the well-being of the whole college community.

Dr. Sweet's interests extended into many fields in addition to her medical activities; she was an expert linguist and historian. She traveled extensively during her summer vacation periods.

She was President of the DeKalb County Medical Society in 1925 and was a member of the Medical Association of Georgia, the Southern Medical and American Medical Associations. She became a Fellow of the American College of Physicians in 1930. She was a member of the Kappa Alpha Theta Sorority and was a loyal member of the Methodist church.

Dr. Sweet was greatly loved and respected by all who were so fortunate as to have been in contact with her. She will be greatly missed by her faculty associates, former students and friends.

CARTER SMITH, M.D., F.A.C.P.,
Governor for Georgia

DR. WALTER M. SOLOMON

Dr. Walter Maximilian Solomon, F.A.C.P., was born in Detroit, July 26, 1900, and died in Cleveland, Dec. 30, 1954, of a brain tumor. He received his Bachelor of Arts degree from Adelbert College in 1931 and his medical degree from Western Reserve University School of Medicine in 1934. He interned at St. Vincent Charity Hospital, 1934–35, and became a resident in City Hospital during the year 1936–37. Following this, he continued on the faculty at Western Reserve University School of Medicine as Demonstrator (1937), Clinical Instructor (1939), Senior Clinical Instructor (1946), and Assistant Clinical Professor of Medicine thereafter. He was a member of the staff of St. Luke's Hospital, beginning in 1937, and Director of the Department of Physical Medicine from 1940 until the time of his death. He was Senior Assistant Visiting Physician at St. Vincent Charity Hospital, and Assistant Visiting Physician to the City Hospital from 1937 to 1954. During World War II, he served in the Medical Corps, AUS, from January, 1942, to March, 1946, with the Fourth General Hospital, stationed in the Pacific Theatre, in charge of the Arthritic Service and Physical Therapy Department. He was separated with the rank of

Lieutenant Colonel. He had been Junior Visiting Physician of the Veterans Administration Hospital since 1946.

A Diplomate of the American Board of Internal Medicine, Dr. Solomon was a former member of the Committee on Education, Council on Physical Therapy of the American Medical Association. He was Chairman of the Editorial Board of the *Archives of Physical Medicine and Rehabilitation.* He contributed to Glasser's *Medical Physics,* Soden's *Rehabilitation of the Handicapped,* and Bierman and Licht's *Physical Medicine in General Practice.* He was a member of the Cleveland Academy of Medicine, Ohio State Medical Association, American Rheumatism Association, American Congress of Physical Medicine and Rehabilitation, American Academy of Physical Medicine, American Society of Physical Therapy Physicians; a member of the staff of the Cleveland Clinic, and a Fellow of the American College of Physicians since 1943.

As a member of the Board of Trustees of the Western Reserve University Medical Alumni Association, the following tribute was written by Dr. Louis Karnosh, a fellow Trustee member, and published in the *Alumni Bulletin,* from which the following selected quotation is taken:

"This contemplation of the life and works of a fellow Trustee of the Medical Alumni Association will be one which is not concerned with the chronological events. It is a commentary or epitaph on the qualities in the man whose memory we respect and whose tragic death we mourn.

"Dr. Solomon's mark in medicine was made in a relatively few years. Educated at Western Reserve Medical School, he chose to live within its immediate aura, to labor as a teacher in his Alma Mater, and to carve out a career within the shadows of its hospitals and laboratories. This he did with the zeal which is well expressed in the quaint and simple Quaker pledge: 'This that we so much esteem and so much adore, is a treasure worth laboring for.'

"It may be said without inviting assail that Dr. Solomon pioneered the cause of Physical Medicine in Cleveland when he organized the department at City Hospital and extended the activities of his specialty to other institutions in Cleveland.

"At the same time his zeal and effort became known in national councils and in the expanded programs which promoted the great cause of rehabilitation. That his enthusiasms about rehabilitation received national acclaim came as a natural sequel, as did a special citation from the President of the United States. These enthusiasms never caused him to be distraught by the tensions of promoting self-enhancement, which nevertheless came to him without effort and as a natural course of events.

"Always piqued and impatient with the pecuniary side of medical practice, which to him interfered with his doctor-patient relationship, this explains according to his own admission his rather drastic resolve to make the change which he did shortly before his death, namely to join an organization which by the reason of its structure relieved him of all concern about the charges he was forced to make to patients for his services.

"His promotion of the cause of Physical Medicine led him into the editorial field and he remained a faithful sounding board for all new developments and devices which advanced the cause of Physical Medicine. In this phase of his many activities he served as chief editor to one periodical and as an associate editor to several others.

"His ubiquity in his field was well demonstrated when at the onset of his only and fatal illness he was scheduled to participate in at least seven programs or seminars where he was invited as a speaker or demonstrator of some of his latest endeavors in

his special field. Some of these involved international associations on Physical Medicine, Rehabilitation and Rheumatism in whose councils and meditations he was no stranger."

The Board of Regents and the Board of Governors of the American College of Physicians extend to the family and friends of Dr. Solomon their sincere sympathy in his untimely death, and wish to record that we held his life work to be an inspiration to all who had the privilege of knowing him, and that we shall revere his memory for the works he accomplished.

CHARLES A. DOAN, M.D., F.A.C.P.,
Governor for Ohio

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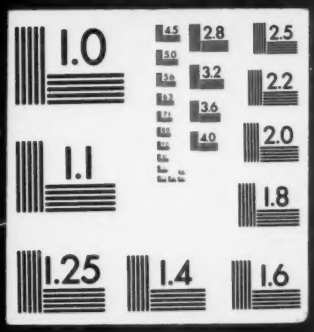
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